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Follicular lymphoma - Section 9

Treatment of high-risk follicular lymphoma

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Take home messages

- The majority of follicular lymphoma (FL) patients diagnosed in 2018 will probably die with the disease and not of the disease—in assessing new regimens, their increased clinical efficacy has thus to be balanced against their adverse effects and quality of life.
- The choice of the right first-line therapy in high-risk FL patients remains an unmet medical need, which has to be addressed in randomized clinical studies. The introduction of new anti-CD20 antibodies and "small molecules" inhibitors targeting intracellular pathways, such as PI3K inhibitors, can be regarded as milestones in FL therapy, prolonging overall survival.

Introduction

A quarter of follicular lymphoma (FL) patients are refractory to first-line immunochemotherapy and/or progress within the first 24 months (POD24), having a 5-year survival rate of <50%.[1] Identification of high-risk patients before first-line therapy is thus an unmet medical need.

Median overall survival (OS) of FL patients exceeds 10 years. Therefore, it is no longer feasible as the primary endpoint of clinical trials. Instead, median progression-free survival (PFS) is an adequate primary efficacy endpoint, especially if supported by objectively assessed improvement of life quality. It varies from 4 to 10 years after first, <2 years after the second and about 1 year after the third and subsequent therapy lines.[2]

Current state of the art

First-line therapy

Immunochemotherapy (chemotherapy in combination with an anti-CD20 antibody; eg, Rituximab [R]) is the standard of care in high-risk FL patients. In an update of FOLL05 trial, 504 advanced FL patients were randomized to R-CVP (Cyclophosphamide, Vincristine, and Prednisone), R-CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) or R-FM (Fludarabine and Mitoxantrone) regimens, all without R-maintenance. None of the regimens was superior with regard to the overall response rate (ORR) or 8-year OS.[3] The 8-year PFS was inferior in R-CVP ($P=0.009$), while nonlymphoma-related mortality was higher in R-FM ($P=0.005$).

R-maintenance after initial immunochemotherapy significantly prolonged median PFS in FL patients as shown. In a long-term follow-up of the PRIMA study (N=1018) where median PFS was 10.49 in patients treated with R-maintenance versus only 4.06 years in patients treated without R-maintenance ($P=0.0001$).[*4] There were, however, no differences in projected median OS. (The 10-year OS was 80%.) Additionally, in low tumor burden FL, similar results to R-maintenance may be obtained by R re-treatment at the time of relapse (RESORT study).[5]

In the GALLIUM study, 1202 previously untreated, advanced FL patients were randomized to R or Obinutuzumab (a second-generation CD20 antibody) immunochemotherapy with subsequent maintenance.[*6] The first evaluation after 41 months revealed that PFS was significantly longer in the Obinutuzumab plus chemotherapy (here: CVP, CHOP, or Bendamustine) arm (hazard ratio 0.68; $P=0.0016$). The POD24 events were reduced from 16.7% to 9.7%. Again, neither median OS nor quality of life was improved. A 3-year PFS was higher in the Bendamustine group, but so was the frequency of adverse events (AE) such as grade 3 to 5 infections, particularly during maintenance. Thus, Bendamustine-based regimens should be used with caution in patients older than 70 years.[*6] Although Obinutuzumab compared with R increased the number of grade 3 to 5 AEs from 69% to 75%, therapy-related deaths were less frequent.

Another alternative in advanced FL is an immunomodulatory regimen R2 (R plus Lenalidomide). In the RELEVANCE study (N=1030), the ORR to R plus Lenalidomide 120 weeks after therapy was fully comparable with R plus chemotherapy.[*7] A 3-year PFS was 77% and 78% for the R2 plus Lenalidomide and immunochemotherapy arms, respectively, with more grade 3 and 4 neutropenia (32% vs. 50%) and febrile neutropenia (2% vs. 7%) in the latter.[*7]

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Table 1

Comparison of Obinutuzumab + Bendamustine and Idelalisib Registration Trials

Characteristics	Obinutuzumab + Bendamustine[10]	Idelalisib[11]
Study group description		
Number of participating patients (all patients/FL)	204/164	125/125
Patients failing 4 or more regimens, %	4	58
Number of prior regimens chemotherapy lines, median [range]	3 [1–8]	4 [2–12]
Median time since completion the previous regimen, mo	3.9	3.9
"Double refractory" to rituximab and alkylating agents, %	77	100
Resistant to Bendamustine, %	0	75
Resistant to the last regimen, %	92	90
After failing ASCT, %		11
Efficacy assessment		
RR, %	65.3	57
Median PFS, mo	33.6	11
Adverse effects		
AE (G3–5), %	65.5	54
Neutropenia, %	34.8	27
Thrombocytopenia, %	10.8	6
Anemia, %	7.4	2
Transaminase elevations, %		13
Diarrhea, %		13
Skin rash, %		2
Infections, %	10.1	9
Thromboses, %		
AE which led to treatment discontinuation, %	20.1	20
SAE, %	43.5	26
Fatal AE, %	7.8	3.2

AE = adverse events, ASCT = allogenic stem cell transplantation, FL = follicular lymphoma, PFS = progression-free survival, RR = relapsed refractory, SAE = serious adverse events.

The risk of FL transformation before introduction of immunochemotherapy regimens was relatively high (28% at 10 years).[8] In a recent, retrospective analysis of 8116 European patients, the 10-year cumulative hazard of transformation was significantly lower (7.7%). The inclusion of R in first-line therapy reduced the risk of transformation significantly ($P=0.003$).[9]

None of the protocols is clearly superior with respect to OS; therefore, the choice of the regimen should be discussed with the patients on individual basis, considering their preferences and possible adverse reactions (infection rate, cytopenias, alopecia, and cardiotoxicity). If there is an evidence of a more aggressive lymphoma, based on histology (Grade 3B), clinical picture (dynamic or asynchronic progression) or PET-CT results R-CHOP should be considered.

Relapsing refractory (R/R) disease

Patients with a late relapse may be re-treated. Those R/R FL patients with POD24, as well as "double refractory patients" (to both alkylator agents and R), should be subjected to an alternative regimen.

Bendamustine with Obinutuzumab (BO) is an effective regimen, best for those who were not treated first-line with Bendamustine. In the GADOLIN study, where 77% of patients were "double refractory," <20% received 3 or more previous regimens, BO allowed to achieve a median PFS of 25.3 months.*[10] In the Idelalisib registration study, median PFS was 11 months, but 100% of patients were "double refractory," 70% resistant to Bendamustine and nearly 60% resistant to at least 3 previous regimens*[11] (Table 1). With a recent approval of the PI3K inhibitors Copanlisib and Duvelisib, followed by a better understanding of pneumonitis and viral infection prophylaxis, PI3K inhibitors became the backbone of R/R FL therapy in third and further therapy lines. Radioimmunotherapy results are still impressive (ORR 57%, median PFS—11 months), although it remains a niche therapy available for specialized centers.[12] Betalutin, a first-in-class antibody radionuclide conjugate which targets CD37 and has an improved efficacy and safety profile is being developed, but is not yet approved. The R2-regimen in R/R FL was explored predominantly in first or second relapse (ORR—76%, median PFS—24 months).[13] Moreover, administering Obinutuzumab with CC-122 (ceroblon inhibitor), a new immunomodulatory agent, revealed comparable response rate and a similar median PFS.[14]

The autologous or reduced-intensity conditioning allogenic stem cell transplants (ASCT, RIC allo SCT) may be considered in R/R cases. An analysis of 197 Grade 3 FL patients revealed that in the first 24 months post-transplant, ASCT was associated with improved OS ($P=0.005$), but in long-time survivors (beyond 24 months) it was associated with inferior OS ($P=0.04$). The increased nonrelapsed mortality of RIC allo SCT (4% vs. 27%, $P=0.001$) was compensated by a lower relapse/progression rate (61% vs. 20%, $P=0.0001$).[15]

Future perspectives

Introducing even better anti-CD20 antibodies and PI3K inhibitors were milestones in FL therapy. Moreover, other novel agents targeting cell surface molecules, intracellular pathways or the microenvironment have been developed and are currently under investigation in clinical trials. For instance, preliminary results, assessed 28 months after a CAR-T cell therapy, are very encouraging with 70% PFS and 93% OS in R/R FL patients who were failing 2 to 10 previous therapy lines.[16]

Overall, treating high-risk FL patients remains a great challenge and enrolling them to clinical studies might be the best way to improve the treatment regimens for these patients.

References

1. Lansigan F, Barak I, Pitcher B, et al. The prognostic significance of PFS24 in follicular lymphoma following first line immunotherapy: a combined analysis of 3 CALGB trials. *Cancer Med*. 2019;8:165–173.
2. Alperovich A, Batlevi C, Smith K, et al. Benchmark of progression free survival for multiple lines of therapy in follicular lymphoma treated in the rituximab era. *Blood*. 2016;128:2955.
3. Luminari S, Ferrari A, Manni M, et al. Long-term results of the FOLL05 trial comparing R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage symptomatic follicular lymphoma. *J Clin Oncol*. 2018;36:689–696.

*4. Salles GA, Seymour JF, Feugier P, et al. Long term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years. *Blood*. 2017;130 (suppl 1):486.

The latest update of PRIMA study, revealing 10.5 year median PFS in a Rituximab based immunochemotherapy followed by maintenance.

5. Williams ME, Hong F, Gascoyne RD, et al. Rituximab extended schedule or retreatment trial for low tumour burden non-follicular indolent B-cell non-Hodgkin lymphomas: Eastern Cooperative Oncology Group Protocol E4402. *Br J Haematol*. 2016;173:867–875.

*6. Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: influence of chemotherapy on efficacy and safety. *J Clin Oncol*. 2018;36:2395–2404.

The latest update of randomised comparison of Rituximab *vs* Obinutuzumab based regimens.

*7. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med*. 2018;379:934–947.

The first randomised trial justyfying a "non-chemo" option in FL.

8. Montoto S, Davies AJ, Matthews J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol*. 2007;25:2426–2433.
9. Federico M, Caballero Barrigon MD, Marcheselli L, et al. Rituximab and the risk of transformation of follicular lymphoma: a retrospective pooled analysis. *Lancet Haematol*. 2018;5:e359–e367.

*10. Cheson BD, Chua N, Mayer J, et al. Overall survival benefit in patients with rituximab-refractory indolent non-Hodgkin lymphoma who received obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN study. *J Clin Oncol*. 2018;36:2259–2266.

The registration randomised study proofing Bendamustine - Obinutuzumab efficacy in R/R FL

*11. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370:1008–1018.

The registration study of the first IP3K inhibitor.

12. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:3262–3269.
13. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (alliance). *J Clin Oncol*. 2015;33:3635–3640.
14. Michot J-M, Ribrag V, Bouabdallah R, et al. 48OCC-122, a novel cereblon-modulating agent, in combination with obinutuzumab (GA101) in patients with relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). *Ann Oncol*. 2018;29 (suppl 3):iii7–iii9. doi: 10.1093/annonc/mdy048.
15. Klyuchnikov E, Bacher U, Woo Ahn K, et al. Long-term survival outcomes of reduced-intensity allogeneic or autologous transplantation in relapsed grade 3 follicular lymphoma. *Bone Marrow Transplant*. 2016;51:58–66.
16. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med*. 2017; 377:2545–2554.