Risk-adapted treatment of follicular non-Hodgkin lymphoma: current standards and future strategies

M. Dreyling, C. Buske, M. Unterhalt, W. Hiddemann
Department of Internal Medicine III. Grosshadern Hospital. Ludwig-Maximilians University. Munich (Germany)

Clinical presentation

Follicular lymphoma (FL) represents 60% of indolent lymphoma (15-25% of all malignant lymphomas) and is thus one the most frequent lymphoma subtypes with a rapidly increasing incidence in Western countries[1]. The vast majority of patients present in advanced stages III or IV (Ann Arbor classification) already at initial diagnosis. The clinical course is characterized by a slowly progressive disease, but continuous relapse pattern with a median overall survival of 5-10 years. Recently, a new prognostic score (FLIPI: Follicular Lymphoma International Prognostic Index) of 5 risk factors including number of nodal areas, LDH, stage, age, and hemoglobin level has been proposed and validated also for patients treated with combined immuno-chemotherapy[2,3]. A "watchful waiting" strategy is generally recommended in patients with low tumor burden and no clinical symptoms, as various randomized trials have demonstrated no benefit of earlier initiation of cytoreductive therapy[4,5]. When FL becomes symptomatic chemotherapy induces remissions in the vast majority of patients but does not prevent relapses and finally refractory disease. Accordingly, survival of these patients has essentially remained unchanged up to the nineties despite exploration of different chemotherapeutic strategies. However, addition of antibody-based strategies has been recently shown to improve overall survival in various prospective trials.

Conventional chemotherapy

The alkylating agents chlorambucil and cyclophosphamide have been the standard approach in indolent lymphoma for decades. Both, daily chlorambucil or repeated courses of CVP or COP (cyclophosphamide, vincristin and prednisone) result in similar progression-free survival (PFS) and overall survival (OS). The addition of doxorubicin (CHOP) led to higher response rates but no longer survival rates[6]. Moreover, potential cardiotoxic effect of doxorubicin has to be considered in a predominantly elderly population.

Purine analogs like fludarabine represent a non-crossresistant alternative to alkylating agents. Although fludarabine is generally well tolerated, the drug is associated with immunosuppression and physicians should be aware of an increased risk of opportunistic infections. Additionally, the cumulative stem-cell toxic effect (especially of > 3 cycles fludarabine) has to be considered if an autologous stem cell transplantation is planned.

Efficacy of fludarabine monotherapy is comparable to alkylating combinations. In comparison to CVP chemotherapy, Fludarabine monotherapy achieved an improved overall response (70 vs. 52%, p = 0.001) and CR rate, but no significant differences of progression-free and overall survival were detected between the two treatment groups[7]. In contrast, fludarabine combinations has achieved impressive remission rates (70-100%) even in relapsed or refractory indolent lymphoma. The most widely investigated fludarabine combinations contain either cyclophosphamide, mitoxantrone or both[8,9].

Bendamustin is another interesting drug without cross-resistance to other alkylating agents, which is chemically related to alkylators, but has a partially different mechanism of action. Monochemotherapy as well as combination with mitoxantrone showed promising response rates of 90% in various phase II studies in patients with refractory or relapsed indolent lymphoma[10,11].

Monoclonal antibodies

Single agent therapy

Rituximab is a chimeric anti-CD20 monoclonal antibody (mAb) which displays an intrinsic anti-lymphoma effect but also triggers CDC (complement dependent cytotoxicity) and ADCC (antibody dependent cellular cytotoxicity), the efficacy of the latter one being strongly dependent on the activation of effector cells via the Fcγ receptor. Accordingly, polymorphisms of this receptor were shown to predict response rate and freedom from progression after Rituximab monotherapy but have been

Table 1. **Rituximab plus chemotherapy in first line therapy of advanced stage follicular lymphoma**

Author	*Regimen*		*p-value*
Hiddemann[16]	**CHOP (205)**	**R-CHOP (223)**	
Response rate	90%	96%	p = 0.011
Median time to treatment failure	31 months	Not reached	p < 0.0001
Overall survival (4 years)	81%	90%	p = 0.039
Marcus[17]	**CVP (159)**	**R-CVP (162)**	
Response rate	57%	81%	p < 0.0001
Median time to treatment failure	7 months	27 months	p < 0.0001
Overall survival (4 years)	77%	83%	p = 0.029
Herold[18]	**MCP (96)**	**R-MCP (105)**	
Response rate	75%	92%	p=0.0009
Median event free survival	29 months	Not reached	p < 0.0001
Overall survival (4 years)	7%	87%	p = 0.0096
Foussard[19]	**12 x CHVP/IFN-α (175)**	**6 x R-CHVP/IFN-α (184)**	
Response rate	85%	94%	p < 0.0001
Median event free survival	Not reached	Not reached	p < 0.0001
Overall survival (3.5 years)	84%	91%	p = 0.029

not confirmed for chemotherapy combinations so far[12].

The high anti-lymphoma activity of rituximab combined with its low toxicity profile was confirmed in the pivotal study of 166 patients with refractory or relapsed indolent lymphoma (mainly follicular type) achieving an overall response rate of 48% (6% CR, 42% PR). However, despite these encouraging results response duration in relapsed patients was limited (12-17 months). Side effects were moderate and consisted mainly of infusion–associated flu-like symptoms[13]. Subsequent clinical trials showed response rates of 70-80% in first line treatment of indolent lymphoma. Interestingly, in this cohort of asymptomatic cases with low tumor burden, CR patients displayed a median progression-free survival of 50 months[14].

Combined immuno-chemotherapy

Based on their different mode of action, *in vitro* data suggested a synergistic activity of conventional chemotherapy and Rituximab. In a small phase II trial the combination of CHOP and Rituximab induced responses in all evaluable patients with a 63% CR rate and an remarkable median PFS of 82 months with 19 of 38 patients still in ongoing remissions[15].

In five large randomized phase III studies a combined immuno-chemotherapy has been compared to chemotherapy alone[16-21] (Table 1). In the trial of the German Low Grade Lymphoma Study Group (GLSG), elderly patients with previously untreated advanced FL received either 6-8 cycles Rituximab plus CHOP (R-CHOP) or chemotherapy alone[16]. R-CHOP was superior with regard to overall response rate (96 vs. 90%; p = 0.01), as well as progression-free survival (p < 0.0001) (Figure 1). Most importantly, combined immuno-chemotherapy significantly improved overall survival after extended follow-up (OS at 4 years: 90 vs. 81%; p = 0.039)[20]. A slight increase of grade 3/4 granulocytopenias was observed in the R-CHOP arm, but rates of (clinically more relevant) infections or other therapy-associated toxicity were similar. Comparable results were reported for the moderately intensive CVP regimen and the more effective MCP schedule (mitoxantrone/chlorambucil/prednison)[17,18]. Interestingly, in a French trial addition of Rituximab resulted in superior survival rates even although chemotherapy were reduced from 12 cycles of a chemotherapy-interferon schedule (CHVP: cyclophosphamide 600 mg/m^2, doxorubicin 25 mg/m^2, etoposide 100 mg/m^2 day 1, prednisone 40 mg/m^2 day 1-5 and interferon-alpha) to 6 cycles of combined immuno-chemotherapy[19]. The superiority of immuno-chemotherapy was also confirmed in patients with recurrent lymphoma. R-FCM (Fludarabine 25 mg/m^2 day 1-3, Cyclophosphamide 200 mg/m^2 day 1-3, Mitoxantrone 8 mg/m^2 day 1) resulted not only in significantly improved response rates and prolonged median progression-free survival, but also overall survival after an extended follow-up[21]. Therefore, in contrast to previous unsuccessful attempts with various chemotherapy regimens, addition of rituximab to conventional chemotherapy improves long term outcome and may even alter the therapeutic aim from palliation only to future, potentionally curative approaches.

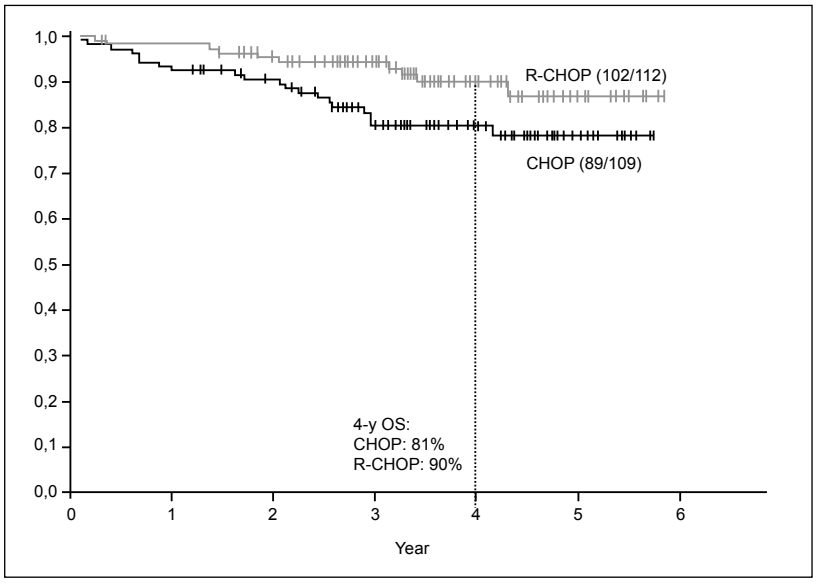

Figure 1. Elderly patients with advanced stage follicular lymphoma were randomized to Rituximab plus CHOP (n = 271) or CHOP (n = 259) only in first line therapy[20].

Radio-immunotherapy

Because of the potential curative effect of external radiation in localized stages, radio-immunotherapy represents an especially promising concept in this disease. Such radio-immunoconjugates are able to deliver high-energy radiation directly to lymphoma cells and also eliminate neighboring bystander cells by a "crossfire effect". The most widely targeted antigen is CD20, which is neither shed nor internalized and thus an appealing target for radio-immunotherapy in B-cell lymphomas. Encouraging results were reported for the ^{90}Y labeled murine antibody Ibritumomab (Zevalin®) and the ^{131}iodine – labeled antibody Tositumomab (Bexxar®). Zevalin® is a pure β-emitter of high energy with a short half-life of 64h and therefore suitable for outpatient treatment.

Both the ^{90}Y-Ibritumomab as well as ^{131}I-Tositumomab induces considerable myelosuppression with a delayed onset 6-10 weeks post treatment. Thus, in case of reduced platelet counts (100-150 000/mm^3) appropriate dose reduction is recommended. Additionally, bone marrow infiltration by lymphoma cells should not exceed 25% because of severe and prolonged myelosuppression.

Although both tracers differ in their half-life and path length, clinical response rate of relapsed follicular lymphoma were comparable (60-80%) in numerous phase II studies. In a long term follow-up of one of the initial trials, this one shot therapeutical approach achieved high response rates with median duration of remissions of more than 5 years in a selected patient population[22]. Of note, only CR patients achieved a long term benefit whereas all PR patients relapsed within 1 year, suggesting CR as a predictive marker for ongoing remissions. Accordingly, current guidelines recommend radioimmunotherapy consolidation after initial tumor debulking by chemotherapy to warrant high CR rates. Following this hypothesis, radioimmunotherapy was applied after CHOP induction in a phase II study of previously untreated FL patients[23]. Estimated 5-year progression-free (67 vs. 44%) and overall survival (87 vs. 64%) were remarkably superior to survival rates after CHOP only in a historical comparison.

Rituximab maintenance

One potential approach to further improve clinical outcome is an extended antibody schedule to provide continuous rituximab exposure. In two clinical trials, the feasibility and efficacy of this approach was confirmed. In the larger trial performed by the Suisse study group, FL patients who did not progress after 4 weekly Rituximab infusions were randomized into a Rituximab maintenance arm (single infusions after 2, 4, 6 and 8 months) versus an observation arm[24]. After a median follow-up of 35 months the event free interval was 23 months in the maintenance arm vs. 12 months in the watch&wait group, respectively (p = 0.02), with an even more pronounced difference in first line patients. Similar results have been reported for a different Rituximab maintenance regime (4 weekly Rituximab infusions every 6 months).

Based on prior experience with interferon maintenance, it was hypothesized that rituximab maintenance may be even more effective after an intensified intial tumor reduction. Thus, two randomized studies evaluated the benefit of Rituximab maintenance after chemotherapy in patients with relapsed follicular lym-

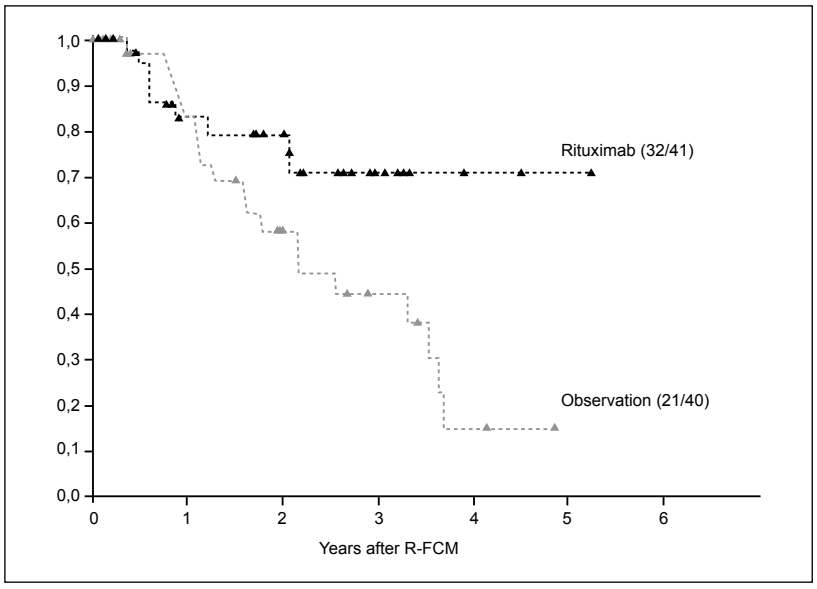

Figure 2. Patients with relapsed follicular lymphoma responding to salvage immunochemotherapy were randomized to Rituximab maintenance (4 weekly doses at months 3 and 9) or observation[21].

phoma[25,26]. In the GLSG trial, rituximab maintenance of 8 additional applications (4 weekly doses after 3 and 9 months) resulted in a remarkable improvement of event-free survival rates (3 y EFS 70 vs. 44%, p = 0.035) (Figure 2) and even borderline effect on overall survival (p = 0.056). No major sided effects of R maintenance were observed in the R maintenance arm and the rate of serious infections was similar in both study arms (p = 0.72) Similarly, in the EORTC trial, a maintenance schedule of 8 single applications every 3 months resulted in almost superimposable survival curves after R-CHOP salvage therapy (median PFS 52 months vs. 23 months in the observation group; p < 0.001) and again a trend to improved overall survival (p = 0.059).

Based on these two large multicenter trials, Rituximab maintenance after combined immunochemotherapy has become the new standard of care in patients with relapsed follicular lymphoma.

Autologous stem cell transplantation (ASCT)

In the last few years three large clinical trials have addressed this issue, however, results were contradictory[27-29]. In a multicenter phase III trial, the GLSG evaluated the effect of myeloablative radiochemotherapy followed by ASCT in comparison to interferon-alpha (IFN-α) maintenance after a CHOP-like induction[27]. Even after prolonged follow-up, ASCT consolidation resulted in a significantly prolonged PFS (5-year PFS: 64.7 vs. 33.3%; p < 0.0001) (Figure 3); however, the median observation time is still too short to provide valid data on overall survival. Of note, myeloablative therapy was associated with only moderate increase of secondary hematological neoplasias (MDS or AML) (5-year risk: 3.8 vs. to 0%; p = 0.025) which was closely related to prior conventional chemotherapy: in the CHOP cohort, only 1.3% of patients developed secondary AML/MDS after 5 years follow-up.

In a similar study of the French GOELAMS study group, consolidating ASCT achieved a significantly superior event-free survival in patients with advanced FL (5 year EFS: 60 vs. 48; p = 0.050; 28); however, overall survival curves were similar due to an unexpected rate of secondary malignancies in contrast to the German study. Finally, the recently published GELA trial did not detect any clinical improvement after myeloablative consolidation as compared to an extended schedule of 12 courses of chemotherapy (CHVP) and IFN-α[29].

Thus, although autologous transplantation has been shown to improve progression-free and overall survival in relapsed follicular lymphoma, data of first line treatment are inconclusive[30]. Additionally, most patients of these studies were treated with chemotherapy only. Therefore, consolidating ASCT has to be reevaluated in comparison to combined immuno-chemotherapy (Figure 3) and currently cannot be recommended as first line treatment outside of clinical trials.

Allogeneic transplantation

Allogeneic transplantation with either conventional myeloablative or reduced intensity conditioning (RIC) remains the only curative treatment approach in patients with advanced FL. The latter approach has substantially reduced acute treatment related morbidity, but longer follow-up demonstrated a high

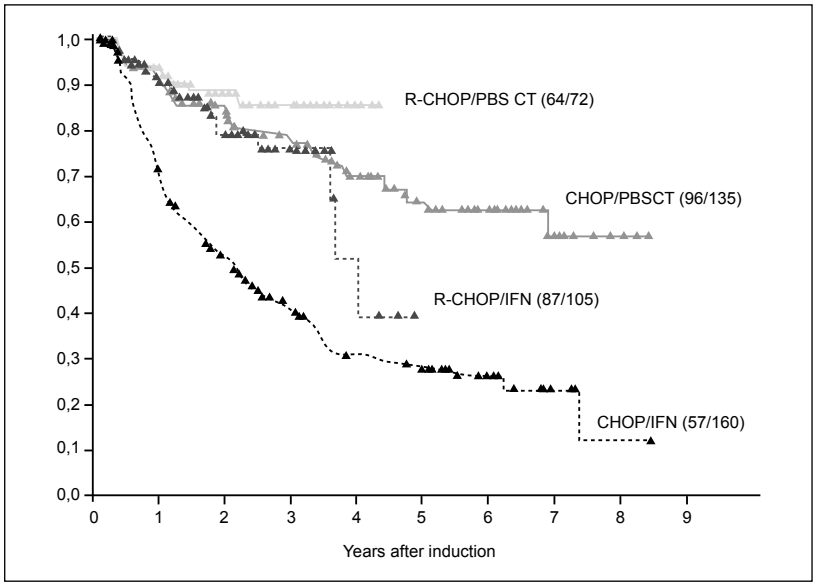

Figure 3. **Patients with advanced stage follicular lymphoma after CHOP+/-R induction were randomized to ASCT or IFN maintenance – historical comparison of two subsequent study generations[16].**

rate of chronic graft-versus-host disease (GvHD) and delayed infectious complications.

The IBMT Registry retrospectively analyzed the clinical outcome in 176 patients with recurrent FL after conventional conditioning and HLA-identical sibling donor transplantation[31]. Only 19% relapses were observed after 1 year and very few recurrences thereafter but treatment-related mortality (TRM) was 24% at 1 year. In the last years, RIC has been increasingly performed because of its significantly lower acute TRM. Khouri *et al*. reported on HLA identical donor allogeneic transplantation with reduced conditioning (fludarabine and cyclophosphamide) in 18 patients with recurrent FL[32]; all patients achieved a CR. Acute GvHD was relatively low but a cumulative incidence of 64% chronic GvHD was observed. Thus, despite improved supportive care within the last decade, even allogeneic transplantation with dose-reduced conditioning is reserved for patients with relapsed follicular lymphoma.

Clinical conclusions

In summary, the implementation of antibody-based strategies has strongly improved the long term outcome of patients with advanced stage follicular lymphoma. For the first time ever, improvement of overall survival was observed after the addition of rituximab to conventional chemotherapy. Besides the proven benefit of rituximab maintenance in relapsed lymphoma, radioimmunotherapy consolidation is another promising approach to achieve complete remissions and potential long term benefit. However, optimal treatment still has to consider the individual performance status and risk profile of the patient. Thus, antibody monotherapy may be discussed for patients with low tumor burden. On the other hand, autologous transplantation may have a role in high risk patients but has to be reevaluated in the era of antibody-based therapeutic approaches. Even more important, the recent improvement of overall survival challenges the concept of watchful waiting; accordingly, current study concepts evaluate the early treatment of asymptomatic patients with follicular lymphoma.

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