Treatment Strategies in Follicular Lymphomas: Current Status and Future Perspectives

Wolfgang Hiddemann, Christian Buske, Martin Dreyling, Oliver Weigert, Georg Lenz, Roswitha Forstpointner, Christina Nickenig, and Michael Unterhalt

ABSTRACT

Although little progress has been made in the treatment of follicular lymphomas (FL) within the last few decades, several new therapeutic modalities have recently demonstrated promising activity. These include myeloablative therapy followed by autologous stem cell transplantation in younger patients in first remission revealing a significant prolongation of remission duration in three prospective randomized trials, whereas the impact on overall survival still needs to be determined. Adding the anti-CD20 antibody rituximab to conventional chemotherapy resulted in a significant increase in remission rate, remission duration and in two of four currently available prospective randomized studies even in a longer overall survival. A prolongation of remission duration was also seen when rituximab was administered as maintenance after cytoreductive therapy or by prolonged application as a single agent. Radioimmunotherapy (RIT) with radioisotopes coupled to monoclonal antibodies revealed encouraging data in several phase II studies. Prospective randomized studies are warranted, however, to define the impact of RIT on FL therapy. New therapeutic perspectives also emerge from increasing insights into the biology of the disease that unravel molecular targets for novel agents, some of which have entered clinical evaluation already.

INTRODUCTION

Follicular lymphoma (FL) is the second most frequent lymphoma subtype worldwide.\(^1\) Prognosis and therapy are closely related to the extent of the disease at initial diagnosis. In less than 15% to 20% of cases, FL is detected at the early stages (I and II). In these patients, radiotherapy is the standard treatment and may result in long-term disease-free survival (DFS) in a sizeable proportion of cases. In the majority of patients, however, the disease is diagnosed at an advanced stage (III or IV) and cannot be cured by conventional therapeutic approaches. For asymptomatic patients with slow-growing disease, a watch-and-wait period following diagnosis may be recommended until the disease becomes symptomatic. In this situation, a broad spectrum of therapeutic options is available, ranging from single-agent to combination chemotherapy. Despite numerous efforts and the exploration of different regimens, chemotherapy has had no major impact on survival and the prognosis of FL has largely remained unchanged over the last decades with median survival times of 8 to 10 years.\(^2,3\)

Recently, new treatment modalities have been developed that justify the hope for improving the long-term outcome of patients suffering from FL. These include, in particular, myeloablative therapy followed by autologous stem cell transplantation (ASCT) and monoclonal antibodies with an inherent antilymphoma activity, as carriers for radioisotopes or as immunotoxins. Future hope is also based on increasing insights into the biology of the disease that may identify molecular targets for novel agents.
ASCT As Salvage Treatment

ASCT was first applied in the setting of relapsed or refractory FL. Encouraging data emerged from several phase II studies, suggesting that this approach may prolong DFS in patients with recurrent, advanced-stage FL. However, the value of ASCT as salvage therapy remains uncertain due to the lack of conclusive phase III data. A three-arm prospective randomized comparison was attempted between conventional salvage therapy, ASCT using purged autologous stem cells, and conventional ASCT with unpurged autologous stem cells, each of which were applied as consolidation after successful re-induction therapy. Recruitment of patients to this trial of which were applied as consolidation after successful

ASCT in First Remission

After having demonstrated the feasibility and potential efficacy of ASCT in the salvage setting, several groups investigated ASCT as consolidation therapy in first remission of advanced stage FL and showed promising long-term results. Most recently, the data from three cooperative group, multicenter, randomized trials have become available (Table 1).

The first study, published by the German Low Grade Lymphoma Study Group (GLSG), randomly compared the effect of myeloablative radiochemotherapy followed by ASCT with interferon-alfa (IFN-α) maintenance (5 million IU three times weekly) in patients 60 years of age with advanced-stage FL. Myeloablation was achieved by total-body irradiation (TBI; 12 Gy) and cyclophosphamide (2 × 60 mg/kg) before re-infusion of unpurged peripheral stem cells. With 240 assessable patients, ASCT consolidation resulted in a significantly longer PFS as compared to IFN-maintenance (5-year PFS rate, 64.7% vs 33.3%, respectively; P < .0001). However, with an overall 5-year survival probability of 84% of all assessable patients, no differences in overall survival have been seen to date.

A second study was reported by the GOELAMS (Groupe Ouest–Est des Leucémies et des Autres Maladies du Sang) study group. This group compared ASCT after VCAP (vindesine, cyclophosphamide, doxorubicin, prednisolone) and IMVP16 (ifosfamide, methotrexate, etoposide) chemotherapy with the combination of CHVP (cyclophosphamide, doxorubicin, teniposide, prednisone) and IFN-α in patients 60 years of age with advanced-stage FL and high tumor burden. As in the German trial, patients received TBI and high-dose cyclophosphamide as conditioning regimen before re-infusion of ex vivo purged peripheral blood stem cells. The event-free survival (EFS) rates at 5 years favored the ASCT arm, with rates of 60% ± 6% versus 48% ± 7% (P = .05). This advantage was restricted, however, to patients with a high risk profile according to follicular lymphoma prognostic index (FLIPI) > 2 (67% ± 9% vs 20 ± 10%; P = .018). Because of a high incidence of secondary fatal cancers in the ASCT arm (n = 7 vs 0), the advantage in EFS did not translate into an improved overall survival in the high-dose treatment group.

A third randomized trial of the GELA (Groupe D’Etudes des Lymphomes De l’Adulte) study group compared six monthly courses of CHVP followed by six courses every 2 months of the same chemotherapy in combination with IFN-α to four courses of CHOP

<p>| Table 1. Results of Myeloablative Therapy With Subsequent (ASCT) in First Remission of Follicular Lymphoma |
|--------------------------------------------------------|----------|---------------------------------|---------|---------|----------|</p>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Induction</th>
<th>Consolidation</th>
<th>EFS (%)</th>
<th>P</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III GLSG</td>
<td>Lenn et al</td>
<td>CHOP/MCP (4-6 cycles)</td>
<td>TBI/Cyclo followed by ASCT (n = 153); IFN-maintenance (n = 154)</td>
<td>64.7 v 33.3*</td>
<td>&lt; .0001</td>
<td>Not yet available</td>
</tr>
<tr>
<td>Phase III GOELAMS</td>
<td>Deconinck et al</td>
<td>VCAP (2-3 cycles)</td>
<td>CHVP/IFNα (6 cycles)</td>
<td>TBI/Cyclo followed by ASCT (n = 80); CHVP plus IFNα (n = 80)</td>
<td>60 v 48†</td>
<td>0.050</td>
</tr>
<tr>
<td>Phase III GELA</td>
<td>Sébèan et al</td>
<td>CHOP (4 cycles)</td>
<td>CHVP/IFNα (6 cycles)</td>
<td>TBI/Cyclo followed by ASCT (n = 192); CHVP plus IFNα (n = 209)</td>
<td>45 v 36‡</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; EFS, event-free survival; OS, overall survival; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; MCP, mitoxantrone, chlorambucil, and prednisone; TBI, total body irradiation; Cyclo, cyclophosphamide; VCAP, vindesine, cyclophosphamide, doxorubicin, and prednisone; IFN, interferon; CHVP, cyclophosphamide, doxorubicin, teniposide, prednisone.

*5-year progression-free survival.
15-year EFS.
17-year EFS.
(cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by high-dose cyclophosphamide, etoposide, and TBI followed by ASCT in untreated patients < 60 years of age with FL and a high tumor burden. A total of 401 patients were entered into the study. In the ASCT arm, 150 patients achieved a complete remission (CR) or partial remission (PR) and were eligible for high-dose therapy and 137 (91%) actually underwent transplantation. The estimated 7-year EFS was 45% for the ASCT arm compared to 36% for the chemotherapy arm (P = .05). However, overall survival was significantly longer for the transplant arm (expected 7-year OS, 74% for the chemotherapy arm v 86% for the transplant arm P = .05). The apparent contradiction of longer overall survival without longer EFS might be explained by imbalances in the intensity and duration of induction therapy.

**Secondary Malignancies After ASCT**

A major concern of applying ASCT to patients with FL relates to the risk of inducing secondary malignancies and in particular secondary acute myeloid leukemias (AML) or myelodysplastic syndromes (MDS). This risk was reported to range from 1% up to 12% in several retrospective nonrandomized analyses including heavily pretreated patients. The three prospective randomized studies mentioned in the preceding section show substantial differences in the risk of secondary AML and MDS ranging from 0% in the GELA study to 3.8% in the GLSG trial to 8.5% in the GOELAMS study. A subgroup analysis of the GLSG study suggests that the risk of secondary MDS or AML may be associated with the type of initial chemotherapy rather than with the conditioning procedure as the risk after MCP (mitoxantrone, chlorambucil, prednisone) was 5.1% at 5 years as compared to 1% after CHOP.

In conclusion, myeloablative radiochemotherapy followed by ASCT is an effective treatment option that prolongs PFS and, potentially, overall survival for younger patients (< 60 years) with advanced-stage FL. Especially after CHOP, the risk of secondary hematologic neoplasias is modest, suggesting the treatment could be offered to young patients with high- or intermediate-risk profiles. As new approaches such as the combination of chemotherapy with rituximab are implemented in multimodality approaches, the role of ASCT may have to be redefined.

**Rituximab Chemotherapy Combinations**

Based on their different modes of action and promising in vitro data, rituximab ± chemotherapy combinations were predicted to have an additive or even synergistic efficacy. This assumption actually proved realistic. In an early phase II trial, the combination of rituximab with CHOP induced responses in all assessable patients with a CR rate of 63% and a median PFS of 82 months.

A prospective randomized comparison of the combination of rituximab plus chemotherapy versus chemotherapy alone was carried out by the GLSG in patients with relapsed FL and mantle cell lymphomas (MCL). In this trial, rituximab was added to the FCM (fludarabine, cyclophosphamide, mitoxantrone) combination and randomly compared with FCM alone. R-FCM revealed a significantly higher remission rate and significantly longer PFS and overall survival for both lymphoma subtypes.

More recently the results of four prospective randomized phase III studies investigating concurrent rituximab plus chemotherapy versus chemotherapy alone have become available (Table 2). In a study by the GLSG, patients with previously untreated advanced-stage FL received either six or eight cycles of rituximab plus CHOP and antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC is mediated by the activation of effector cells via the Fcγ receptor. Accordingly, two polymorphisms of this receptor were shown to predict response rate and freedom from progression after rituximab monotherapy. Other potential mechanisms of action include the induction of apoptosis, a block of the G1,S-transition, an impairment of differentiation and an increased phosphorylation of cellular proteins.

Several phase II clinical trials in fact demonstrated a significant single-agent activity of rituximab in previously treated and, later, in untreated FL patients. Despite these encouraging results response duration after the “standard” course of rituximab administered once a week for 4 weeks at a dose of 375 mg/m² to patients at relapse is limited (12 to 17 months). Hence, a prolongation of the drug schedule was investigated in a prospective randomized phase III study by the SAKK (Schweizer Arbeitsgemeinschaft fu¨r Klinische Krebsforschung). In this trial, patients with FL who did not progress after four weeks of once-weekly rituximab infusions were randomized into a rituximab maintenance arm by single infusions at 3, 5, 7 and 9 months versus observation only. After a median observation time of 35 months, the EFS was significantly longer in the maintenance arm (23 v 12 months; P = .02). This effect was even more pronounced in chemotherapy-naive patients (P = .009). Similar results were reported for a different rituximab maintenance regimen comprising 4 weeks of once-weekly rituximab infusions, which was repeated after 6 months.

**Single-Agent Therapy**

The only currently available unconjugated monoclonal antibody (mAb) with proven activity in FL is rituximab. Rituximab is a chimeric anti-CD20 mAb that was shown to lyse CD20+ cells by complement activation and antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC is mediated by the activation of effector cells via the Fcγ receptor. Accordingly, two polymorphisms of this receptor were shown to predict response rate and freedom from progression after rituximab monotherapy. Other potential mechanisms of action include the induction of apoptosis, a block of the G1,S-transition, an impairment of differentiation and an increased phosphorylation of cellular proteins.

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(R-CHOP) or CHOP alone. R-CHOP was superior with regard to overall response rate (96% vs 90%; \( P = .011 \)), as well as PFS (\( P = .0006 \)). In addition, overall survival was prolonged (\( P = .016 \)). In the R-CHOP arm, a 10% increase of grade 3/4 granulocytopenia was observed, but rates of infections and other therapy-associated adverse effects were similar. In another international phase III trial, the addition of rituximab to the CVP (cyclophosphamide, vincristine, and prednisone) regimen resulted in a significant improvement of response rates (81% vs 57%; \( P < .0001 \)) as well as of PFS (\( P < .0001 \)) as compared to CVP alone. A third trial by the OSHO (Ostdeutsche Studiengruppe für Hämatologie und Onkologie) was based on the MCP combination (mitoxantrone, chlorambucil, and prednisone). As in the preceding trials a significant improvement of response rates and PFS was seen. Similar results also emerged from the most recent study by the GELA adding rituximab to the CHVP plus IFN-\( \alpha \) regimen in high tumor burden—patients.

The Eastern Cooperative Oncology Group (ECOG) applied a different strategy. In a recently completed randomized phase III study, remission induction by CVP was followed by rituximab maintenance over 2 years, or observation only. The maintenance rituximab resulted in a median 2.7-year prolongation of PFS (\( P = .0003 \)). In conclusion, all available randomized studies consistently show that rituximab has a significantly beneficial effect in patients with advanced stage follicular lymphoma either when administered in addition to initial chemotherapy or as maintenance after cytoreductive therapy without rituximab or by prolonged application as a single agent. These results could lead to the conclusion that it is no longer the question whether rituximab should be applied for first line therapy of advanced stage follicular lymphomas, but rather how. However, further studies, some of which are in progress, are needed to address this question in greater detail according to age, other prognostic factors, and the FLIPI. In this context, R-CHOP may be the preferred treatment option in patients with poor-risk disease for whom more intense treatment is required to achieve and sustain remission. Patients with lesser-risk disease or for whom a less intense treatment is indicated due to comorbidities may be better suited for single-agent rituximab or R-CVP.

Because of the inherent high radiosensitivity of FL and the expression of potential target antigens on the cell surface radioimmunoconjugates (RIT) represent an especially promising concept in this disease. At present, the majority of radioimmunoconjugates target the CD20 antigen, which is expressed on most B-cell lymphomas. Radiolysis is induced in both the targeted cells and adjacent lymphoma cells due to the radiation crossfire effect, which may be especially advantageous for treating bulky, poorly vascularized tumors and those with heterogeneous antigen expression.

So far, most clinical experience has been gained with two different radioimmunoconjugates, the Yttrium-90 (\( ^{90}\text{Y} \))—labeled murine antibody ibritumomab and the iodine-131 (\( ^{131}\text{I} \))—labeled antibody tositumomab. \( ^{90}\text{Y} \)-ibritumomab is a pure \( \beta \)-emitter of high energy with a short half-life of 64 hours and is therefore suitable for outpatient treatment. \( ^{131}\text{I} \)-tositumomab delivers both \( \beta \) and \( \gamma \) irradiation with a half-life of 8 days, therefore shielding of persons in contact is necessary (Table 3). Both constructs may be applied in a nonmyeloablative as well as a myeloablative dosage.

In the nonmyeloablative approach, both conjugates demonstrated comparable activity with response rates of 60% to 80% and CR rates from 15% to 44%. Notably, CRs have been durable, even among heavily pretreated patients. In a randomized trial, a single infusion of

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<th>Regimen</th>
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<tr>
<td>Hiddemann et al\textsuperscript{27}</td>
<td>CHOP [n = 205]</td>
<td>R-CHOP [n = 223]</td>
</tr>
<tr>
<td>Response rate</td>
<td>90%</td>
<td>96%</td>
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<td>Median time to treatment failure</td>
<td>31 months</td>
<td>Not reached</td>
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<tr>
<td>Marcus et al\textsuperscript{28}</td>
<td>CVP [n = 159]</td>
<td>R-CVP [n = 162]</td>
</tr>
<tr>
<td>Response rate</td>
<td>57%</td>
<td>81%</td>
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<tr>
<td>Median time to treatment failure</td>
<td>7 months</td>
<td>27 months</td>
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<tr>
<td>Herold et al\textsuperscript{29}</td>
<td>MCP [n = 96]</td>
<td>R-MCP [n = 105]</td>
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<tr>
<td>Response rate</td>
<td>75%</td>
<td>92%</td>
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<td>Median event-free survival</td>
<td>19 months</td>
<td>Not reached</td>
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<tr>
<td>Salles et al\textsuperscript{30}</td>
<td>CHVP/IFN-( \alpha ) [n = 175]</td>
<td>R-CHVP/IFN-( \alpha ) [n = 184]</td>
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<tr>
<td>Response rate</td>
<td>85%</td>
<td>94%</td>
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<tr>
<td>Median event-free survival</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Hochster et al\textsuperscript{31}</td>
<td>CVP [n = 157]</td>
<td>CVP + R [n = 148]</td>
</tr>
<tr>
<td>Median event-free survival</td>
<td>17 months*</td>
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</tbody>
</table>

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab plus CHOP; CVP, cyclophosphamide, vincristine, and prednisone; MCP, mitoxantrone, chlorambucil, and prednisone; CHVP, cyclophosphamide, doxorubicin, teniposide, and prednisone; IFN-\( \alpha \), interferon alfa.

*After maintenance random assignment.
90Y-ibritumomab was superior to a standard four weekly infusion of rituximab with regard to overall response (80% vs 56%) and CR rate (30% vs 16%). Although the median PFS was not different in the total cohort, a long-term benefit was observed for patients achieving a complete remission after 90Y-ibritumomab. Recently, Kaminski et al. reported that 131I-tositumomab resulted in a 95% response rate with 75% CR in first line therapy of FL. Although these results were obtained in patients with a very favorable prognostic profile, the fact that more than half of the cases remained in a continuous CR after a minimum follow-up of more than 4 years strongly supports further testing of this approach in prospective randomized studies.

Of note, both radioimmunoconjugates induce considerable myelosuppression with delayed nadirs occurring 6 to 10 weeks post-treatment. Both treatments are limited to patients with bone marrow infiltration by lymphoma cells < 25% because of the risk of severe, prolonged myelosuppression.

Myeloablative radioimmunotherapy with subsequent re-infusion of autologous peripheral stem cells has been successfully applied in patients with refractory or relapsed FL. A single myeloablative dose of 131I-tositumomab achieved an overall response rate of 93% with a CR/unconfirmed CR (CRu) rate of 85% and an estimated 5-year PFS and overall survival of 48% and 67%, respectively, results comparing favorably to historical controls treated with high-dose chemotherapy. Importantly, the risk for secondary hematologic neoplasias did not differ between the two treatment strategies and were estimated to be 7.6% at 8 years for RIT and 8.6% at 7 years for chemotherapy alone. Several studies have demonstrated that radio-immunotherapy can be combined with high-dose chemotherapy as a preparatory regimen and phase III trials are now in progress to definitively test the value of this approach.

Besides single agent RIT this approach may also be combined with conventional chemotherapy as consolidation in remission. Applying such a combination Press et al. reported response rates of 67% CR/CRu and 23% PR in a phase II study with 131I-tositumomab in previously untreated FL patients. Importantly, in 27 of the 47 patients the remission status was converted to CR after the infusion of the radioconjugate. After a median follow-up of 2.3 years, the estimated 2-year PFS was 81%, with a 2-year overall survival of 97%. Again, the main adverse effect was reversible myelosuppression, which was less severe than after the previous chemotherapy (CHOP).

Hence, RIT represents a highly attractive and promising approach for the treatment of FL. However, comparison with other treatment modalities in way of prospective randomized studies is warranted to define the role and the way and timing of RIT in the overall strategy of FL therapy.

### NEW AGENTS AND FUTURE APPROACHES

Active immunotherapy in FL is an attractive approach given the fact that the hypervariable region of the immunoglobulin receptor represents a tumor-specific target. Vaccination strategies have resulted in encouraging results such that definitive phase III trials are in progress. This approach is discussed elsewhere in this series. Other new approaches to treatment are discussed by O’Connor in this issue of the Journal of Clinical Oncology. A major challenge will be how to best integrate these approaches into existing treatment algorithms.

### Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.
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