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Current treatment strategies in follicular lymphomas

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Introduction and background

Follicular lymphoma (FL) is the second most frequent lymphoma subtype worldwide [1]. Its incidence is rapidly increasing in Western countries and has nearly doubled within the last three decades.

In less than 15–20% of patients FL is detected at the early stages I or II. In these patients radiotherapy is the treatment of choice and is applied as extended or involved field irradiation that results in long-term disease-free survival (DFS) and probable cure in approximately 45–80% of patients.

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. Hence, anti-lymphoma therapy is usually withheld for a watch and wait period until the disease becomes symptomatic. In this situation a broad spectrum of therapeutic options is available ranging from single agent to combination chemotherapy. In spite of numerous efforts and the exploration of different regimens, chemotherapy has had no major impact on survival and the prognosis of FL has literally remained unchanged over the last decades with a median survival time of 8–10 years [2, 3].

Recently, new treatment modalities have been developed which 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 anti-lymphoma activity or as carriers for radioisotopes or immunotoxins.

Myeloablative therapy with subsequent autologous stem cell transplantation (ASCT)

After the feasibility and potential efficacy of ASCT was demonstrated in patients with relapsed disease [4–8] ASCT was investigated as consolidation therapy in first remission of advanced stage FL and showed promising long-term results. Most recently, the data of three cooperative group, multicenter randomized trials have become available. They consistently show a significant prolongation of response duration while data on overall survival are different (Table 1).

In the first study that was published by the German Low Grade Lymphoma Study Group (GLSG) the median observation time is still too short to judge the impact of ASCT on overall survival [9]. In the study by the French GOELAMS (Groupe Ouest–Est des Leucémies et des Autres Maladies du Sang) study group a high incidence of secondary malignancies was observed in the ASCT arm resulting in a similar survival duration in both treatment arms [10]. In contrast, the trial of the GELA (Groupe D’Etudes des Lymphomes De l’Adulte), revealed a significantly longer overall survival for the transplant arm [11].

One of the major reasons for these differences appears to be secondary malignancies and in particular secondary acute myeloid leukemias (AML) or myelodysplastic syndromes (MDS) after ASCT. Several retrospective non-randomized analyses reported an incidence of 1% up to 12% [12, 13]. More valuable results can be derived from the afore-mentioned three prospective randomized studies. They show substantial differences in the risk of secondary AML and MDS being 0% in the GELA study, 8.5% in the GOELAMS study and 3.8% in the GLSG trial. 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. Hence, after cytoreduction with MCP (Mitoxantrone, Chlorambucil, Prednisone) the risk was 5.1 % at 5 years as compared to only 1% after CHOP [14].

Hence, myeloablative radiochemotherapy followed by ASCT is an effective treatment option for young patients (<65 years) with advanced stage FL lymphoma, which improves response duration and potentially also overall survival. Especially after a CHOP-like induction therapy, the increase of secondary hematologic neoplasias is moderate and acceptable and should not preclude the offer of such treatment to young patients with a high or intermediate risk profile. As new approaches such as the combination of chemotherapy with monoclonal antibodies and particularly with Rituximab are implemented in multi-modal approaches the role of ASCT may have to be redefined.

Anti-lymphoma antibodies with inherent anti-lymphoma activity

The only currently available anti-lymphoma antibody with a widely proven activity in FL is the monoclonal antibody (mAb) Rituximab. Several phase II clinical trials demonstrated a significant single agent activity of Rituximab given every week at a dose of 375 mg/m²/d in pretreated as well as in previously untreated patients with FL although response duration was relatively short (12–17 months) [15–19]. Response duration
could be prolonged by continued application of Rituximab in remission as a maintenance therapy [20, 21].

Based on these promising results Rituximab was combined with chemotherapy and a first phase II trial on the combination of Rituximab with CHOP showed responses in all evaluable patients with a complete remission (CR) rate of 63 % and a median PFS of 82 months [22].

The first 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 which was randomly compared with FCM alone. R-FCM revealed a significantly higher remission rate, a significantly longer PFS and particularly overall survival for both lymphoma subtypes [23].

Most recently the results of four prospective randomized phase III studies investigating Rituximab plus chemotherapy versus chemotherapy alone have become available (Table 2) [24–27]. They consistently show that the addition of Rituximab to different chemotherapeutic regimens results in a significant increase in response rates, time to treatment failure and response duration. In the study by the GLSG comparing Rituximab plus CHOP (R-CHOP) or CHOP alone even overall survival was prolonged [24].

A different strategy was applied by the Eastern Cooperative Oncology Group (ECOG). In a recently completed randomized phase III study remission induction by CVP was followed by Rituximab maintenance over 2 years or observation only. By Rituximab maintenance a 2.7 year longer PFS was achieved (P =) [28].

Two recently reported trials investigated the efficacy of Rituximab maintenance after R-chemotherapy in patients with relapsed FL. The first study by the GLSG was based on the previously mentioned R-FCM regimen [29] while the EORTC/Intergroup study used R-CHOP for salvage treatment [30]. In both trials a significant prolongation of response duration was observed.

In conclusion, all available randomized studies consistently show that Rituximab has a significantly beneficial effect in patients with advanced stage follicular lymphoma either when given in addition to initial chemotherapy or as maintenance after cytoreductive therapy with and without Rituximab or by prolonged application as a single agent. It is therefore no longer the question whether Rituximab should be applied for first-line

Table 1. Results of prospective randomized trials on myeloablative therapy with subsequent autologous stem cell transplantation (ASCT) in first remission of follicular lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Induction</th>
<th>Consolidation (number of patients)</th>
<th>Event-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III Lenz et al. (GLSG) [9]</td>
<td>CHOP/MCP (4–6 cycles)</td>
<td>TBI/Cyclo followed by ASCT (n = 153) IFN-maintenance (n = 154)</td>
<td>64.7% versus 33.3%* (P &lt;.0001)</td>
<td>Not yet available</td>
</tr>
<tr>
<td>Phase III Deconinck et al. (GOELAMS) [10]</td>
<td>VCAP (2–3 cycles) CHVP/IFN-α (6 cycles)</td>
<td>TBI/Cyclo followed by ASCT (n = 86) CHVP plus IFN-α (n = 80)</td>
<td>60% versus 48%* (P &lt;.050)</td>
<td>Median not reached in both treatment arms</td>
</tr>
<tr>
<td>Phase III Sebban et al. (GELA) [11]</td>
<td>CHOP (4 cycles) CHVP/IFN-α (6 cycles)</td>
<td>TBI/Cyclo followed by ASCT (n = 192) CHVP plus IFN-α (n = 209)</td>
<td>45% versus 36%§ (P = 0.5)</td>
<td>86% versus 74% (7-year OS)</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; EFS, event-free survival; OS, overall survival. TBI, total body irradiation; Cyclo, cyclophosphamide. 5-year PFS; + 5-year EFS; § 7-year EFS.

Table 2. Rituximab plus chemotherapy in first-line therapy of advanced stage follicular lymphoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen (number of patients)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiddemann et al. [24]</td>
<td>CHOP (205) R-CHOP (223)</td>
<td>P = 0.011</td>
</tr>
<tr>
<td>Response rate</td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td>Median time to treatment failure</td>
<td>31 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>Marcus et al. [25]</td>
<td>CVP (159) R-CVP (162)</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Response rate</td>
<td>57%</td>
<td>81%</td>
</tr>
<tr>
<td>Median time to treatment failure</td>
<td>7 months</td>
<td>27 months</td>
</tr>
<tr>
<td>Herold et al. [26]</td>
<td>MCP (96) R-MCP (105)</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Response rate</td>
<td>75%</td>
<td>92%</td>
</tr>
<tr>
<td>Median event-free survival</td>
<td>19 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>Salles et al. [27]</td>
<td>CHVP/IFN-α (175) R-CHVP/IFN-α (184)</td>
<td>P &lt;0.0001</td>
</tr>
<tr>
<td>Response rate (CR/Cru)</td>
<td>85% (49%)</td>
<td>94% (76%)</td>
</tr>
<tr>
<td>Median event-free survival</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>
therapy of advanced stage follicular lymphomas but rather how. Although further studies are needed to address this question in greater detail it may be speculated that the different ways of application might not be used competitively but rather complementary and might be appropriate for different patient populations as defined by age, performance status, international prognostic index (IPI) or the recently introduced IPI for follicular lymphoma (FLIPI) [31].

anti-lymphoma antibodies as carriers for radio-isotopes (Radio-Immunotherapy)

Because of the inherent high radiosensitivity of FL and the expression of potential target antigens on the cell surface radio-immunotherapy (RIT) represents an especially promising concept in this disease. At present, the majority of radio-immunoconjugates target the CD20 antigen which is expressed on most B cell lymphomas and is neither shed nor internalized thus representing an appealing target for RIT. 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 radio-immunoconjugates, the Yttrium-90 (\(^{90}\text{Y}\))-labeled murine antibody Ibritumomab (Zevalin®) and the Iodine-131 (\(^{131}\text{I}\))-labeled antibody Tositumomab (Bexxar®). \(^{90}\text{Y}\)-Ibritumomab is a pure \(\beta\)-emitter of high energy with a short half-life of 64 h 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 non-myeloablative as well as myeloablative dosage.

In the non-myeloablative approach both conjugates demonstrated comparable activity with response rates of 60–80% and complete response (CR)/complete remission uncertain (CRu)-rates between 15–44% [32]. Most recently Kaminski et al. reported that \(^{131}\text{I}\)-Tositumomab induced high response rates of 95% with 75% CR in first-line treatment [33]. Although these results were obtained in patients with a very favorable prognostic profile the fact that more than half of the patients 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.

Myeloablative radio-immunotherapy with subsequent re-infusion of autologous peripheral stem cells has been successfully used in patients with refractory or relapsed FL.

<table>
<thead>
<tr>
<th>Source of Radiation</th>
<th>(^{90}\text{Y})-Ibritumomab (Zevalin®)</th>
<th>(^{131}\text{I})-Tositumomab (Bexxar®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (MeV)</td>
<td>(\beta)</td>
<td>(\beta) and (\gamma)</td>
</tr>
<tr>
<td>Depth of activity (mm)</td>
<td>2.3</td>
<td>0.36 / 0.61</td>
</tr>
<tr>
<td>Half life (h)</td>
<td>64</td>
<td>193</td>
</tr>
<tr>
<td>Application</td>
<td>Out-patient</td>
<td>In-patient (radioprotection)</td>
</tr>
</tbody>
</table>

A single myeloablative dose of \(^{131}\text{I}\)-Tositumomab achieved an overall response rate of 93% with a CR/CRu rate of 85% and an estimated 5-year PFS and overall survival (OS) of 48% and 67%, respectively, in comparison to 29% and 53% after high-dose chemotherapy [34]. 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% partial response (PR) in a phase II study with \(^{131}\text{I}\)-Tositumomab in previously untreated FL patients [35]. After a median follow-up of 2.3 years, the estimated 2-year PFS was 81% with a 2-year OS of 97%.

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 definite role and the way and timing of RIT in the overall strategy of FL therapy.

new agents and therapeutic approaches

biologic agents

FL is characterized by a translocation between the chromosomes 14 and 18 that brings the \(bcl-2\) gene under the transcriptional control of the immunoglobulin heavy chain promoter. Resulting overexpression of the Bcl-2 protein can be detected in the vast majority of FL and has been associated with cellular resistance to apoptosis and chemotherapy [36]. Specific inhibition of gene expression can be achieved by chemically modified single-strand DNA molecules with a nucleotide sequence complementary to that of their target mRNA. Oblimersen (formerly known as G3139) is an 18-mer phosphorothioate oligonucleotide targeting the first six codons of the \(bcl-2\) mRNA open reading frame. A dose escalating study of oblimersen administered as a 14-day subcutaneous infusion in 21 patients with advanced, relapsed Bcl-2 positive non-Hodgkin’s lymphoma (NHL) including nine cases of FL demonstrated feasibility and suggested clinical activity [37]. Based on promising in vitro data ongoing studies currently explore the combination of oblimersen with Rituximab [38].

The ubiquitin-proteasome pathway is essential for maintaining intracellular protein homeostasis, thus representing a valid target in the treatment of malignant disease. At the center of this degenerative pathway is the 26S proteasome, an ATP-dependent multicatalytic protease. Various oncoproteins and regulatory proteins for cell cycle progression and apoptosis are processed by this pathway including p53, p21, p27, nuclear factor kappa B (NFkB) and Bcl-2 [39]. Bortezomib is a potent, selective, reversible inhibitor of the 26S proteasome and demonstrated clinical activity in relapsed multiple myeloma. Encouraging data were also observed in patients with other lymphoproliferative malignancies, including FL and MCL [40, 41]. Preliminary data from a phase II trial indicate that responses may continue to occur until several months after the end of treatment [42]. Bortezomib is currently explored in several phase II studies that also explore its combination with other cytostatic agents such as liposomal doxorubicin [43].
Another interesting agent is the orally available dipeptidyl peptidase inhibitor (PT-100, Talabostat), which acts via novel immune mechanisms by up-regulated gene expression of certain cytokines within the hematopoietic tissue [44, 45].

adoptive immunotherapy

Active immunotherapy in FL aims for generation of a humoral and/or cellular immune response of the host against highly specific lymphoma antigens. The hypervariable region (idiotype, Id) is unique to each lymphoproliferative clone, representing an attractive target for vaccination strategies. A recent retrospective analysis of 136 patients with FL who received Id vaccination following chemotherapy demonstrated anti-Id responses in 47% and significantly prolonged PFS (8.21 versus 3.38 years, \( P = 0.018 \)) in those with detectable idiotype-specific humoral immune response [46]. Efficacy of this approach might be further improved by adding granulocyte macrophage stimulating factor (GM-CSF) for enhanced induction of T-cell response [47]. Probably the optimal setting for vaccination strategies is the minimal residual disease (MRD) state with adequate recovery of immune effector mechanisms after chemotherapy. Improved manufacturing methods are being developed to make these individualized vaccines feasible for more widespread use.

In the light of constantly increasing clinical experience with novel therapeutic agents there is justified optimism to shift treatment towards pathogenesis-oriented and lymphoma-specific approaches. Whether this will translate into impact on natural history of FL remains to be awaited. Obviously further comparative clinical trials are desperately needed, as clinicians will have to face the challenge of how to best integrate these exciting new options into existing established treatment algorithms.

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