Introduction

Important progress has been made in the management of patients with non-Hodgkin’s lymphoma (NHL). With the rapid advent of monoclonal antibodies including radioimmunoconjugates and further immunotherapeutic strategies such as miniallotransplants and anti-idiotype-vaccinations we now have many new therapeutic options. Prognostic indices such as the International Prognostic Index (IPI) and variations thereof, sophisticated genetic microsatellite profiles or new diagnostic tools such as positron emission tomography (PET) will help to further optimise treatment selection and treatment evaluation. The former REAL and now WHO classification is internationally accepted and defines different clinically relevant entities of NHL. But for the time being, most clinical study reports rely on the old algorithm of ‘indolent’ and ‘aggressive’ NHL histology grouping and for practical reasons we follow this approach and will highlight some relevant data on mucosa-associated lymphoid tissue (MALT), mantle cell, primary mediastinal and CNS NHL.

Indolent non-Hodgkin’s lymphoma

The various types of indolent NHLs, encompassing follicular NHL, small lymphocytic lymphoma (SLL), lymphoplasmacytic NHL and marginal zone lymphoma, including MALT-type and mantle cell lymphoma, behave in distinct ways. But they share several common features of mature B-lymphocytes, including expression of mature surface antigens CD19, CD20 and CD22. Mantle cell NHL with the typical translocation t(11;14) leading to an overexpression of the cyclin D1 gene shows a poor prognosis with the worst overall survival rate of only 27% at 5 years.

New cytostatics or drug combinations for indolent NHL

Gemcitabine, a molecule resembling arabinoside, is included in a variety of ongoing combination trials as are a few other new analogues, such as navelbine and liposomal doxorubicin and oxaliplatin. Gemcitabine in combination with bleomycin and alkylating agents has shown severe pulmonary toxicity in 30% of patients [1].

The purine analogues fludarabine and 2-chlorodeoxyadenosine (2-CDA) have previously shown high activity in most indolent lymphoma types as monotherapy, in combinations or combined modality therapy. Most of these trials have been performed in pretreated patients. The European Organisation for Research and Treatment of Cancer (EORTC) group has now compared single-agent fludarabine to CVP (cyclophosphamide, vincristine and prednisone) combination therapy in 381 non-pretreated patients with stages III and IV indolent NHL. For 248 of 380 patients enrolled, chemotherapy was started immediately whereas for 133 patients a ‘wait and see’ approach was chosen. Although the response rate is significantly higher after fludarabine there is no significant increase in time to treatment failure (TTF) or overall survival (OS) (Table 1; [2]).

Monoclonal antibodies in the treatment of indolent NHL

The chimeric monoclonal antibody against CD20 rituximab was the first ever monoclonal antibody approved by the FDA for the treatment of relapsed follicular NHL. Rituximab showed significant activity as a single agent in previously treated patients with a high response rate of 48% and a median time to progression of 13 months [3]. The response rate was independent of the number of pretreatments even for patients relapsing after autologous stem-cell transplantation. In treatment naive patients there are now several studies reporting on the therapeutic activity of rituximab monotherapy. Hainsworth

Table 1. EORTC trial fludarabine versus CVP first line in indolent NHL patients [2]

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Response rate %</th>
<th>TTF (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CR</td>
</tr>
<tr>
<td>Fludarabine (ALL)</td>
<td>68</td>
<td>38</td>
</tr>
<tr>
<td>Watch and wait</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Immediate therapy</td>
<td>74</td>
<td>46</td>
</tr>
<tr>
<td>CVP (ALL)</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>Watch and wait</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Immediate therapy</td>
<td>53</td>
<td>15</td>
</tr>
</tbody>
</table>

CR, complete response; CVP, cyclophosphamide, vincristine and prednisone; NHL, non-Hodgkin’s lymphoma; OR, overall response; PR, partial response; TTF, time to treatment failure.
et al. [4] reported a 47% response rate [7% complete responses (CRs), 40% partial responses (PRs)] with an additional 48% of patients having stable disease or a minor response. Patients received a maintenance dose of rituximab every 6 months and the progression-free survival at 2 years was 67%. Also the overall response rate at 15 months had risen to 65% (27% CRs) which suggests an important further improvement in response with maintenance rituximab. Colombat reported a 73% overall response rate with 33% CRs and 47% PRs on day 78 after starting therapy with rituximab and the response rate after 1 year increased to 80% (41% CRs [5]). The Swiss Lymphoma Group presented a monotherapy induction study with rituximab and randomisation for a maintenance therapy (4 × rituximab every 2 months) in responding patients versus no further treatment [6]. Time to relapse was significantly higher in the group of patients with maintenance therapy and was even doubled in non-pretreated patients (18 versus 36 months; Table 2).

The first humanised rat derived anti-CD52 mAb CAMPATH-1H (alemtuzumab) registered for patients with refractory chronic lymphocytic leukemia (CLL) is active in refractory NHL patients as is the humanised mAb against CD22 (epratuzumab) and both can be successfully combined with rituximab.

Radioimmunoconjugates

Indolent NHLs are highly radiosensitive and radioimmunoconjugates act also on CD20 negative neighbouring cells, in poorly vasculated tissue as well as in immunosuppressed patients. The radio-immunoconjugate zevalin [a murine anti-CD20 monoclonal antibody (ibritumomab)] is a pure β-emitter and can be administered on an outpatient basis. In a randomised phase III trial (n = 143) patients received either rituximab or 90Y-ibritumomab: the overall response for the radioimmunoconjugate was 80% versus 44% for rituximab alone. The patients who were not responsive or refractory to rituximab were enrolled in an additional trial and treated with ibritumomab with an overall response rate of 46% [10].

Bexxar (tositumomab) is an anti-CD20 mAb of murine origin linked to iodine 131 which requires a prolonged stay in a specialised inpatient setting but yields a high rate of prolonged CRs in pretreated NHL patients [11]. Bone marrow toxicity is dose limiting for both radioimmunoconjugates. It is likely that they will have their primary indication in consolidation after induction or in combination with chemotherapy.

Monoclonal antibodies or radioimmunoconjugates combined with chemotherapy as initial treatment for indolent NHL

Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab was studied in 40 patients with ≥75% of them being chemotherapy naïve. A response rate of 100% including 63% CRs was documented. Follow-up shows that 75% of patients remain relapse free at 65.1 months. The same group reported on the combination of fludarabine in conjunction with rituximab and showed as expected a high response rate with 80% CR and 13% PR. Because of hematological toxicity a dose reduction of fludarabine was necessary and due to a high rate of herpes zoster infections (17%) acyclovir was administered prophylactically [12].

In another study, CHOP was compared to fludarabine combined with mitoxantrone (FM) followed by rituximab. In this Italian study 78 of 150 patients were evaluable for response. CR and PR were 66% and 27% in the FM arm versus 41% and 51% in the CHOP arm. After rituximab courses the molecular remission was 61% (FM) and 41% (CHOP) for the Bcl-2/lgH chimeric gene [13]. An ongoing multicentric prospective randomised trial is comparing FCM (fludarabine, cyclophosphamide and mitoxantrone) with and without

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>Duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maloney et al. [7]</td>
<td>34</td>
<td>50</td>
<td>9</td>
<td>10.2</td>
</tr>
<tr>
<td>McLaughlin et al. [3]</td>
<td>118</td>
<td>60</td>
<td>6</td>
<td>13.0</td>
</tr>
<tr>
<td>Davis et al. [8]</td>
<td>22</td>
<td>55</td>
<td>NR</td>
<td>8.0</td>
</tr>
<tr>
<td>Foran et al. [9]</td>
<td>70</td>
<td>46</td>
<td>3</td>
<td>11.0</td>
</tr>
<tr>
<td>Hainsworth et al. [4]</td>
<td>25</td>
<td>52</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Colombat et al. [5]</td>
<td>50</td>
<td>73</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Ghelmini et al. [6]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo naïve</td>
<td>58</td>
<td>66</td>
<td>9</td>
<td>18.3/36</td>
</tr>
<tr>
<td>Pre-treated</td>
<td>128</td>
<td>46</td>
<td>8</td>
<td>11/14</td>
</tr>
<tr>
<td>Overall</td>
<td>50–60</td>
<td>5–10</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

*Without and †with maintenance rituximab.

CR, complete response; OR, overall response; NR, not reported.
rituximab in relapsing or refractory patients with follicular or mantle cell lymphoma [14]. All patients have previously been treated with a CHOP regimen. In the first analysis of 80 of 147 patients the CR rate of FCM treated patients was 15% whereas the CR rate with the combination with rituximab was 36%, the overall response rate was 53% and 89%, respectively. Remarkably CRs in mantle cell lymphoma patients were only observed in the FCM/rituximab group (46%).

The South West Oncology Group (SWOG) 9800 study [15] reported on CHOP followed by rituximab in low grade NHL. This phase II study investigated the value of rituximab given after six standard cycles of CHOP, given every 21 days in patients achieving CRs or PRs at the end of six cycles. Patients with bulky (>10 cm in a single dimension) stage II–IV disease were eligible. Of the 104 patients registered 74 received subsequent rituximab therapy. The CR rate increased from 37 to 54%, the PR rate decreased from 35 to 18% with no plateau in the survival curve at a median follow-up of 2.7 years. There is now a SWOG three-arm study ongoing comparing CHOP versus CHOP/rituximab versus CHOP/tosilumomab in newly diagnosed patients with follicular NHL. Furthermore an Italian trial has started comparing CVP versus CVP/rituximab.

Radioimmunotherapy with yttrium-90-ibritumomab and iodine-131-tositumomab has shown activity in all lymphoma histologies. CHOP, followed by iodine-131-tositumomab as first-line treatment for follicular NHL, has also been studied in a SWOG trial [18]. An 80% response rate was achieved in the 71 evaluable patients (52% CR, 28% PR).

Table 3 summarises results obtained with three different combinations of monoclonal antibodies with CHOP.

**MALT and marginal zone lymphomas**

Marginal zone lymphomas have a preference for extranodal involvement. Gastric MALT lymphoma (40% of all MALT lymphomas) in individuals infected with *Helicobacter pylori* is now a paradigm for studying the pathogenesis of chronic antigen stimulation leading to a mucosa-associated lymphoma. The eradication of *H. pylori* with antibiotics combined with an antacid results in eradication of *H. pylori* in 90% of cases and a clinical remission in about two-thirds of patients, usually those patients with a gastric low grade MALT lymphoma with a predominant small cell component. True molecular remission is documented in <50% of patients [19].

A recent study from Germany has shown that the translocation t(11;18) deregulates the expression of two genes (*HP12* and *MALT*) which renders B-cells genetically stable and highly unlikely to undergo progression to diffuse large B-cell lymphoma. This new finding might guide us in the future to select patients for more aggressive initial therapy [20].

In non-responding or relapsing patients as well as more advanced stage patients chemotherapy with chlorambucil or fludarabine is active in the majority of patients with identical CR rates. CHOP might be preferable in patients with a more aggressive histology as shown by a high percentage of large cells or an advanced and bulky disease. Therapy with rituximab has not yet been studied in representative trials. Total gastrectomy or radiotherapy is reserved for those patients with localised resistant disease.

Patients with non-gastric MALT lymphomas can be treated by local resection, radiotherapy or chlorambucil but large prospective trials are missing.

**Mantle cell lymphoma**

There is no standard treatment for patients with this eventually resistant lymphoma. Most responding patients only achieve an incomplete and short lasting response and die after 3.4 years. CHOP or fludarabine did not improve these results but rituximab showed an approximately 30% response rate in relapsing patients. Promising results have been achieved with the combination of CHOP and rituximab with a 90% OR including 50% CRs but event-free survival was not prolonged to that commonly reported. Therefore intensive first-line chemotherapy such as Hyper-CVAD, autologous and nonmyoablative allogeneic transplantation are now intensively studied [21, 22]. With the addition of rituximab for in vivo purging before peripheral stem cell harvesting it is hoped that the response quality can be further improved. High-dose radioimmunotherapy with rituximab bound to 131-iodine is another promising approach reported by the Marburg group [23]. But many patients with this disease are not fit enough to receive such intensive treatments and less aggressive treatments such as oral PEP-C might be more appropriate. Today the best option is to include eligible patients in clinical trials since none of the treatment options so far has been convincingly shown to improve the final outcome of these patients.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Partial response rate (%)</th>
<th>Complete response rate (%)</th>
<th>Overall response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP plus rituximab [16]</td>
<td>42</td>
<td>58</td>
<td>100</td>
</tr>
<tr>
<td>CHOP→rituximab [17]</td>
<td>18</td>
<td>54</td>
<td>72</td>
</tr>
<tr>
<td>CHOP→iodine-131-tositumomab [18]</td>
<td>28</td>
<td>52</td>
<td>80</td>
</tr>
</tbody>
</table>

NHL, non-Hodgkin’s lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.
Aggressive NHL.

The majority of the patients with an aggressive histology NHL have a diffuse large B-cell lymphoma (DLCL) and one-third present with localised disease and approximately 40% show an extranodal involvement. Only patients achieving a complete remission after initial therapy will have a good chance of cure in 60–70% of cases. The age adjusted prognostic index (IPI) is the most useful measure of prognosis. The primary mediastinal lymphoma as well as primary CNS NHL deserve special discussion with respect to the best treatment options currently available.

Treatment of early stage aggressive NHL (stage I or II)

Long-term results have been presented in two large studies, one from the Eastern Cooperative Oncology Group (ECOG) [24] and one from SWOG [15] comparing CHOP chemotherapy with or without radiation in patients with early stage aggressive lymphoma. In the ECOG study 352 patients with early stage disease were accrued. In group 1 patients received CHOP for eight cycles and only PR patients received 40 Gy to the involved field. Patients in group 2 received eight cycles of CHOP followed by 30 Gy to the involved field in CR patients and 40 Gy to the involved field in PR patients. The overall rate of complete response was 61%, with partial response seen in 28%. The addition of 40 Gy involved field radiotherapy was able to convert 28% of the PR patients to CR status. Although the addition of involved field radiation improved relapse rate within the irradiated field, this did not translate to an overall survival benefit at 10 years [24]. In a multivariate analysis, only two factors were associated with a statistically decreased time to progression: the presence of three or more sites of disease and a poor performance status. The SWOG presented long-term follow-up data on a group of 401 patients with limited-stage aggressive NHL. They were randomised to receive eight cycles of CHOP or three cycles of CHOP followed by involved field radiation, using a minimum of 40 Gy and a maximum of 55 Gy [15]. The results after 8.4 years show an excess of lymphoma relapses and lymphoma-related deaths in the group that received three cycles of CHOP plus radiation. A stage adapted Prognostic Index was developed (Table 4).

<table>
<thead>
<tr>
<th>No. of poor prognostic factors</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-Year</td>
</tr>
<tr>
<td>None</td>
<td>95</td>
</tr>
<tr>
<td>1, 2</td>
<td>71</td>
</tr>
<tr>
<td>≥3</td>
<td>50</td>
</tr>
</tbody>
</table>

Adverse prognostic factors: age ≥60 years; bulky (>10 cm); stage II; elevated lactate dehydrogenase (LDH), performance status ≥1. NHL, non-Hodgkin’s lymphoma; NA, not applicable.

Therefore the recommendation for the time being is to use CHOP × 3 with involved field radiotherapy only in patients with no such risk factors. A recent study report from the Groupe d’Etude des Lymphomes de l’Adulte (GELA) showed no role for involved field radiotherapy after four cycles of CHOP in elderly patients with localised aggressive lymphoma but rather a trend for a negative impact on survival [25]. For patients <60 years of age without risk factors, Adriamycin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) improved the overall survival significantly as compared with CHOP plus involved field radiotherapy (P = 0.02; OS 5-year survival 89% versus 80% [26]).

Advanced stage aggressive NHL.

CHOP- or CHOP-like chemotherapy regimens are considered the ‘golden standard’ for the treatment of an average patient with advanced stage aggressive NHL of mostly diffuse large B-cell lymphoma histology. But this golden standard has now been successfully challenged at least for the group of elderly patients whose age ranges from 60 to 80 years. The GELA group compared CHOP with CHOP plus rituximab in a group of 399 elderly patients with ages ranging from 60 to 80 years with diffuse large B-cell NHL [27]. The results at a median follow-up of 2 years showed statistically significant superiority of CHOP/rituximab with an approximately 10% difference in overall survival and a 20% disease-free survival advantage.

In a large German multicentre study of 831 patients 2-weekly CHOP with granulocyte colony-stimulating factor (G-CSF) support showed superiority to standard CHOP or CHOP/etoposide combinations in newly diagnosed patients with aggressive NHL ≥60 years of age. At a median observation time of 40 months OS was significantly better for 2-weekly CHOP (64.3% versus 49%) and was the best tolerated arm in this milestone study [28]. As a next step, this intensified CHOP regime will now be compared to the same treatment combined with rituximab. This trial is ongoing in different European countries (RECOVER-60 study). In a recent report from the GELA group, survival in elderly patients with aggressive lymphoma could also be improved on the using of ACVBP followed by sequential methotrexate/leucovorin, ifosfamide, etoposide and Ara-C in comparison to standard CHOP (LNH 93-5 study; P = 0.013) but with a significantly higher toxic death rate [29].

Overall upfront primary high-dose chemotherapy regimens with autologous stem-cell support have not yet been shown to be more curative than CHOP or CHOP-like regimens alone. This has been challenged by the French cooperative Groupe Ouest-Est des Lymphomes de l’Adulte (GOELAMS) in a recent study of patients <60 years of age with an IPI excluding the high risk group. They found a significantly better OS at 5 years for the intermediate high risk group (P = 0.005; OS 74% versus 43%) for the frontline high-dose chemotherapy arm as compared with standard CHOP × 8 but only a trend for the good risk group [29a]. Therefore this
field is still open for randomised clinical studies such as the Multicenter International Study on the Treatment of Aggressive Lymphomas (MISTRAL) trial in Europe [30].

**Primary mediastinal lymphoma**

This thymus derived type of aggressive NHL is clearly different from diffuse large B-cell lymphoma (DLCL) and presents in rather young adults with a rapidly growing mediastinal mass. CHOP, CHOP-like or MACOP-B-like (MACOP-B, methotrexate, adriamycin, cyclophosphamide, oncovin, prednisone-bleomycin) regimes have been used in only small groups of patients and due to the lack of prospective randomised trials we do not know the relative benefits of these primary treatment approaches. Although cure rates of 38–88% have been claimed, so far the overall impression is that the cure rate is the same as for DLCL patients overall. This is disappointing since these patients tend to be young with a good performance status and an initially localised disease of the mediastinum and almost never have bone marrow involvement. The value of mediastinal consolidation radiotherapy is very questionable since radiotherapy in patients relapsing in the mediastinum only did not yield any durable remissions. In a recently published review of primary mediastinal B-cell lymphoma the authors have outlined the rather favourable outcome in relapsing and refractory patients after salvage high-dose chemotherapy with stem-cell support. Their conclusion was to consider high-dose chemotherapy with stem-cell support in patients with residual disease after initial chemotherapy or PET-positive residual mass [31]. Obviously there is an urgent need for clinical trials in order to optimise treatments for this disease.

**Primary CNS NHL**

Patients with primary CNS lymphoma tend to have a poor prognosis and there is no consensus with respect to standard treatment. High-dose methotrexate-based chemotherapy is widely used with different dosages and scheduling and the addition of intrathecal therapy seems of no further benefit. The role of radiotherapy is questioned since it frequently contributes to neuropsychological malfunctioning, especially in elderly patients. In a recent Italian multicentre study including 370 patients radiotherapy in methotrexate-treated patients did not improve the survival in patients with a CR after chemotherapy [32]. Also, the dose chosen for high-dose methotrexate did not correlate with survival. Radiotherapy alone as compared with chemotherapy followed by radiotherapy was clearly inferior. The best results were obtained in patients treated with a combination of methotrexate and high-dose cytarabine. Systemic cytarabine and rituximab are both clearly active in CNS NHL, but how they will contribute in the future is not yet defined [33].

**Treatment after relapse of aggressive NHL**

Although the majority of relapsing patients will respond to salvage chemotherapy, only 20–30% will have a CR and only <10% will achieve a more durable response lasting >3 years with a chance of cure. Intensive chemotherapy with autologous stem-cell support has become the standard therapy for patients typically aged <65 years with disease still responsive to salvage therapy. Primary refractory patients or patients not responding to salvage therapy have so far no chance of cure with a standard salvage approach and should therefore be candidates for experimental treatments, such as standard or reduced intensity conditioning followed by allogeneic bone marrow transplantation. Many elderly patients or patients with a poor performance status will not be eligible for such an approach. They should receive palliative chemo- and/or radiotherapy according to clinical need.

**Conclusions**

For most patients with indolent NHL, long-term survival with a good quality of life is the primary goal of therapy. For aggressive NHL patient cure is still the target of therapy and a CR is a prerequisite to achieve this goal. Salvage therapy needs more aggressive experimental treatment approaches including high-dose chemo-immunotherapy, and in selected cases, allogenic stem-cell transplantation. With the advent of monoclonal antibodies, anti-idiotype vaccinations and other new modalities, good clinical practise requires our readiness to enter patients in well-designed prospective clinical trials. Only such an approach will increase the median survival and cure rate of a still increasing population of patients diagnosed with NHL in this new century.

**References**


