

# THE R-EVOLUTION IN NON-HODGKIN'S LYMPHOMA THERAPY

## How rituximab and other treatment advances are improving outcomes

Douglas A. Stewart, MD, FRCPC

### Top-line summary

Three major therapeutic advances during the 20<sup>th</sup> century improved survival rates of adults with non-Hodgkin's lymphoma (NHL): the use of external beam orthovoltage radiotherapy for early-stage NHL,<sup>1</sup> CHOP chemotherapy for aggressive-histology NHL,<sup>2</sup> and high-dose chemotherapy with autologous stem cell transplantation (HDCT/ASCT) for relapsed NHL.<sup>3</sup> Some disappointments included lack of survival benefit for several approaches: immediate vs delayed chemotherapy in patients with asymptomatic advanced-stage indolent NHL,<sup>4</sup> intensive combination chemotherapy regimens over single-agent chemotherapy for indolent NHL,<sup>5</sup> and dose-intensive 3<sup>rd</sup> generation chemotherapy regimens or front-line HDCT/ASCT over conventional CHOP for aggressive histology NHL.<sup>6,7</sup>

Recently, a 4<sup>th</sup> major advance in NHL management has become evident: the development of effective immunologic therapy with the chimeric anti-CD20 monoclonal antibody rituximab.<sup>8</sup> Other encouraging developments in NHL include:

- the revised WHO pathologic classification for lymphoid malignancies<sup>9</sup>
- the promise for further refinements through lymphoma genome profiling<sup>9,10,11</sup>
- prognostic scoring systems which may help stratify patients to receive different treatment strategies<sup>12,13</sup>
- functional imaging with FDG-positron emission tomography (PET)<sup>14</sup>
- radioimmunoconjugate therapy (RIT)<sup>15</sup>

Here, *Oncology Exchange* reviews these recent advances in the context of the most common NHL subtypes.

**Douglas A. Stewart, MD, FRCPC** is Associate Professor in the Departments of Oncology and Medicine, University of Calgary and Tom Baker Cancer Centre, Calgary, AB. Address for correspondence: 1331-29<sup>th</sup> Street NW, Calgary, AB T2N 4N2; Tel: (403) 944-2080; Fax: (403) 283-1651; Email: douglast@cancerboard.ab.ca

Canadian cancer statistics rank NHL as 5<sup>th</sup> in cancer frequency and 6<sup>th</sup> in cause of cancer death.<sup>16</sup> Both the incidence and mortality rates increased slightly over the past decade.

Diagnosis and subtyping of NHL requires an adequate tissue biopsy as it is based on light microscopic interpretation complemented by special stains, immunophenotyping and cytogenetics. See the box on page 5 for a treatment-oriented histologic classification based on the WHO system. **Table 1** (page 6) divides the most common lymphoma subtypes into different prognostic groups by 5-year survival rates.

### DIFFUSE LARGE B-CELL LYMPHOMA

The most common lymphoma subtype worldwide is diffuse large B-cell lymphoma (DLBCL), representing approximately 30% of all NHL cases.<sup>9,17</sup> Median age at presentation is 64 years (range 14-98), with 55% being men. Approximately 50% present at Stage 3-4, 30% have bulky disease mass > 10 cm, and 15% are marrow-positive.

### Advanced stage DLBCL

Until the advent of rituximab, CHOP (cyclophosphamide 750 mg/m<sup>2</sup> IV Day 1, doxorubicin 50 mg/m<sup>2</sup> IV Day 1, vincristine 1.4 mg/m<sup>2</sup> [max 2 mg] IV Day 1 and prednisone 100 mg po Days 1-5, with cycles repeated q 21 days) was the most widely used combination chemotherapy regimen for DLBCL, conferring 5-year progression-free survival (PFS) and overall survival (OS) rates of 35% and 45%, respectively. The International Prognostic Index (IPI) for aggressive NHL can be used to refine prognostication;<sup>1</sup> factors include age > 60 years, Eastern Cooperative Oncology Group (ECOG) performance status 2-4, disease Stage 3-4, more than 1 extranodal site of involvement and elevated serum lactate dehydrogenase (LDH). The 5-year PFS rates following 6-8 cycles of CHOP-like chemotherapy for patients with 0-1, 2-3 and 4-5 factors are approximately 60%, 30% and 15%, respectively, and OS rates approximate 70%, 45% and 25%. Three recently-described approaches to improve upon the results of CHOP chemotherapy include the addition of rituximab to CHOP (R-CHOP), dose-dense delivery of CHOP q 14 days



with granulocyte-colony stimulating factor (G-CSF) support, and HDCT/ASCT consolidation treatment (i.e. given after induction therapy) for patients with poor-prognosis DLBCL.

Three randomized controlled trials (RCTs) evaluating R-CHOP have been reported. In 2002, the GELA (Groupe d'Etude des Lymphomes de l'Adulte) published results comparing R-CHOP vs CHOP in 399 DLBCL patients aged 60–80 years.<sup>18</sup> The R-CHOP regimen in this study involved rituximab 375 mg/m<sup>2</sup> IV on Day 1 of each cycle of CHOP. Significant improvements were seen in rates of complete remission (76% vs 63%), 2-year time to treatment failure (58% vs 40%) and 2-year OS (72% vs 60%), without significant increases in toxicity. Updated results project 5-year OS rates of 58% vs 45% in favour of R-CHOP with benefit seen in both low- and high-risk IPI subgroups. A 632-patient US Intergroup study randomized patients over age 60 years to CHOP or R-CHOP (using a different schedule of rituximab), followed by a 2<sup>nd</sup> randomization of responding patients to observation or rituximab maintenance (4 doses q 6 months x 2 years).<sup>19</sup> Significant improvement in PFS was seen for R-CHOP over CHOP induction, as well as for rituximab maintenance over no maintenance in the subgroup of patients who received CHOP-only induction. Finally, the MInT study evaluated R-CHOP vs CHOP in 823 DLBCL patients < 60 years of age with low-risk IPI scores;<sup>20</sup> 72% had Stage 1 or 2 disease and 49% had bulky disease. Updated results of MInT reported at the December 2004 American Society

of Hematology Annual Meeting showed a 2-year PFS of 80% vs 61% ( $p < 0.0001$ ) and OS of 95% vs 86% ( $p = 0.0002$ ) in favour of R-CHOP over CHOP.

The German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) conducted studies comparing CHOP-21 (CHOP in 21-day cycles), CHOP-14 (14-day cycles), CHOEP-21 (CHOP + etoposide) and CHOEP-14 in patients less than 60 years of age (NHL-B1)<sup>21</sup> and over 60 years (NHL-B2).<sup>22</sup> OS improved with CHOP-14 over CHOP-21 for patients > 60 years old (53% vs 41%) and < 60 years old (85% vs 79%) while CHOEP improved event-free survival only for younger patients with normal LDH levels (69% vs 58%), but had no impact on OS. The OS benefit of administering CHOP-14 requires confirmation from additional RCTs before it should be considered the optimal administration schedule.

RCTs evaluating 1<sup>st</sup> remission-consolidation with HDCT/ASCT for poor-prognosis DLBCL have reported conflicting results.<sup>7,23</sup> Many studies were frankly negative, while a few showed significant PFS benefits from HDCT. These studies had some serious shortcomings: many had inadequate statistical power, most did not use IPI as an eligibility or stratification criterion, and there was tremendous heterogeneity between studies with respect to histologic subtypes, choice of standard and HDCT regimens and timing of HDCT relative to number of induction chemotherapy cycles. Further, up to 40% of patients in the HDCT arms never received the assigned HDCT, often due to an inadequate response to abbreviated induction chemotherapy prior to planned HDCT/ASCT (a strategy not considered viable for future trials). The American Intergroup and the Clinical Trials Group of the National Cancer Institute of Canada (NCIC CTG) are currently conducting a more definitive HDCT study that enrolls aggressive-histology NHL patients with adverse IPI risk scores. Those who respond to 5 cycles of R-CHOP chemotherapy are randomized to 1 more R-CHOP followed by HDCT/ASCT or to 3 more cycles of R-CHOP. If the study meets accrual targets, it should be adequately powered to definitively

address the role of late 1<sup>st</sup>-remission consolidation with HDCT/ASCT.

Overall, the weight of evidence strongly supports the use of R-CHOP as the current standard of care in treating adults with DLBCL, regardless of

## DISCOURSE

### Classification of non-Hodgkin's lymphoma<sup>9</sup>

#### B-CELL LYMPHOMAS

##### Indolent

- Follicular
- Small lymphocytic (CLL)
- Mantle cell
- Marginal zone extranodal, MALT
- Marginal zone, nodal
- Splenic marginal zone
- Lymphoplasmacytic (Waldenström's macroglobulinemia)

##### Aggressive

- Diffuse large B-cell
- Mediastinal (thymic) large B-cell
- Intravascular large B-cell
- Primary effusion

##### Special

- Burkitt
- Precursor B-lymphoblastic
- HIV-associated (+ KSAV pleural)
- Post-transplant lymphoproliferative disorder

#### T-CELL LYMPHOMAS

##### Indolent

- Mycosis fungoides
- Primary cutaneous anaplastic large cell (CD30+)

##### Aggressive

- Peripheral T-cell, unspecified
- Anaplastic large cell (CD30+)
- Angioimmunoblastic (AILD)
- Extranodal NK/T-cell (nasal type)
- Enteropathy-type
- Hepatosplenic
- Subcutaneous panniculitis-like

##### Special

- Precursor T lymphoblastic
- Adult T-cell leukemia/lymphoma (ATL/L-HTLV-1+)

## Beyond the IPI

The international **Leukemia-Lymphoma Molecular Profiling Project** has used cDNA microarray techniques to identify a more favourable germinal centre signature and a less favourable activated peripheral blood lymphocyte signature which have prognostic significance independent of the IPI in DLBCL.<sup>10</sup> These different signatures can be identified using immunophenotyping to detect protein expression. For example the activated B-lymphocyte signature is associated with BCL-6 and CD10 negativity, as well as BCL-2, CD138, and MUM1 positivity, while the converse is true for germinal centre phenotype. Ongoing research is evaluating whether these markers may be used with the IPI to more accurately determine prognosis and optimize therapy.<sup>11</sup>

age, stage or prognostic subgroup. Future studies are needed to evaluate the potential added benefit of maintenance rituximab, HDCT/ASCT consolidation for poor prognostic subgroups, dose-dense scheduling of R-CHOP every 14 days with G-CSF instead of every 21 days as conventionally administered, and the incorporation of rituximab into salvage therapy protocols, including salvage HDCT/ASCT. Another approach worthy of study involves multiple cycles of high-dose sequential induction chemotherapy.<sup>24</sup>

### Early-stage DLBCL

The modified IPI for non-bulky Stage 1–2A DLBCL includes the following factors: age > 60 years, ECOG status 2–4, Stage 2, and elevated LDH. The 5-year PFS rates for patients with 0, 1–2 and 3–4 factors who are treated with 3 cycles of CHOP-like chemotherapy and involved field radiation therapy (IFRT) are approximately 95%, 80% and 60%, respectively.<sup>25</sup> Patients with bulky Stage 1–2 DLBCL

have a 5-year PFS rate of only 50%. Therefore, Stage 1–2 DLBCL patients with bulky disease or 3–4 adverse risk factors are probably best treated with more prolonged chemotherapy regimens, similar to advanced-staged patients.

Conventional therapy in North America for non-bulky Stage 1–2A DLBCL is based on a Southwest Oncology Group study (SWOG 8736) that reported 5-year PFS of 77% vs 64% and OS of 82% vs 72% in favour of CHOP x 3 + IFRT compared to CHOP x 8.<sup>26</sup> Unfortunately, long-term followup of this study documented excess relapse outside the radiation field beyond 5 years in the CHOP x 3 + IFRT arm, resulting in loss of PFS benefit at 7 years and loss of OS benefit at 9 years after treatment.<sup>27</sup> The latter finding suggested the need for more effective systemic therapy than CHOP x 3.

Although no RCTs have evaluated R-CHOP vs CHOP for early-stage DLBCL, the Phase 2 trial SWOG 0014 evaluated 3 cycles of R-CHOP + IFRT

for 62 DLBCL patients who had either Stage 1 disease and 1 adverse IPI prognostic factor or non-bulky Stage 2 disease.<sup>28</sup> At median followup of 2.4 years, this trial demonstrated 2-year PFS of 94% — superior to the 85% 2-year PFS rate seen in a matched historical control group of 68 patients from SWOG 8736 who received CHOP + IFRT without rituximab. This non-randomized comparison supports the current practice of R-CHOP x 3 + IFRT for limited stage DLBCL.

### Relapsed DLBCL

Several salvage chemotherapy regimens exist for relapsed DLBCL, but they haven't been evaluated in RCTs. Most involve prolonged intravenous administration, necessitating hospitalization. The GDP (gemcitabine, dexamethasone, cisplatin) regimen can easily be administered on an outpatient basis, and was reported by the NCIC CTG to give a 49% response rate in 51 patients with relapsed/refractory NHL.<sup>29</sup> The NCIC CTG LY.12 trial is currently evaluating DHAP (dexamethasone, high-dose Ara-C, cisplatin) vs GDP salvage therapy for relapsed/refractory aggressive NHL. Responding patients undergo HDCT/ASCT and then a 2<sup>nd</sup> randomization between observation and rituximab consolidation therapy every 2 months for 1 year.

The only RCT of high-dose vs conventional-dose salvage chemotherapy for relapsed, chemosensitive NHL demonstrated a significant failure-free survival (51% vs 12%) and OS (53% vs 32%) advantage for high-dose BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) and ASCT.<sup>3</sup> Unfortunately, HDCT is not generally feasible in patients older than 65 years, in those with rapidly progressive, chemoresistant disease (especially with central nervous system or extensive marrow involvement), or in those who mobilize inadequate numbers of blood stem cells. For patients who are eligible, however, it is critically important to offer HDCT/ASCT because it dramatically improves outcome.

New effective treatments are needed for patients with relapsed DLBCL, especially those who are not transplant candidates. Unfortunately, reports so

*continued on page 8*

**TABLE 1. Lymphoma subtypes according to prognosis**

5-Year OS	Indolent*	Aggressive
> 70%	Follicular Extranodal marginal zone of MALT	Anaplastic large T/null cell (CD30+, ALK+)
40% to 70%	Small B-lymphocytic Lymphoplasmacytic Nodal marginal zone	Diffuse large B-cell Primary mediastinal large B-cell Burkitt and Burkitt-like
< 40%	Mantle cell	Peripheral T-cell Precursor T-lymphoblastic

\* Indolent lymphoma: lymphoma associated with a median survival of at least 3 years but not associated with a plateau on Kaplan-Meier PFS and OS curves following conventional chemotherapy.

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far of radiolabelled anti-CD20 antibody therapy are somewhat disappointing. The largest multicentre Phase 2 study evaluating RIT with Y90 ibritumomab tiuxetan in 104 elderly patients with relapsed DLBCL reported an overall 44% response rate and 6-month median PFS. In the 28 patients who were initially treated with rituximab-containing chemotherapy, the response rate was only 19% and median PFS was 1.6 months.<sup>30</sup>

## FOLLICULAR LYMPHOMA

Follicular lymphoma (FL) is the 2<sup>nd</sup> most common type of lymphoma worldwide, representing approximately 20% to 25% of all NHL cases.<sup>9,17</sup> The median age at diagnosis is approximately 60 years (range 20–90). Roughly 65% of patients have Stage 3–4 disease, 50% have bone marrow involvement and 90% have an ECOG performance status of 0–1 at diagnosis.<sup>17</sup> Although the median survival of patients with FL is between 8–10 years, there is marked variability in clinical course from spontaneous remission to aggressive, treatment-resistant progression. The Follicular Lymphoma International Prognostic Index (FLIPI) includes the following 5 adverse prognostic factors: age  $\geq$  60 years, Stage 3–4, elevated LDH, hemoglobin less than 120 g/L, and 5 or more involved nodal areas.<sup>13</sup> Approximate 5- and 10-year OS rates are 90% and 70% for patients with 0–1 FLIPI risk factors, 75% and 50% for 2 factors, and 50% and 35% for 3–5 factors, respectively.<sup>13</sup>

### Early-stage FL

Current standard treatment for limited-stage FL usually consists of radiotherapy to the involved nodal region and possibly the immediately adjacent uninvolved region. With this approach, 10–20-year PFS is approximately 30% to 50%.<sup>31</sup> Approaches under investigation for early-stage FL include the use of watchful waiting, combined modality therapy, RIT and the use of PET imaging to attempt more accurate definition of localized disease.<sup>14,32</sup>

### Low tumour-burden advanced-stage FL

Watchful waiting is the standard recommendation for the 50% of advanced-

staged FL patients without significant symptoms, bulky lymphadenopathy, massive splenomegaly, cytopenias or impending organ compromise at diagnosis. Despite significantly higher complete response (CR) and PFS rates, RCTs have not demonstrated a significant OS benefit of immediate over delayed chemotherapy for asymptomatic FL.<sup>4,33</sup> Such differences in CR rates, however, may become important to maximize potential benefits of maintenance monoclonal antibodies, vaccine therapy or RIT. An important ongoing study in low tumour-burden advanced-stage FL is the E4402 American Cooperative Group study called the RESORT trial (Rituximab Extended Schedule Or Re-Treatment). RESORT randomizes low tumour-burden, rituximab-responsive indolent lymphoma patients to either scheduled rituximab every 3 months until relapse, or to observation followed by rituximab retreatment at relapse. The results will hopefully determine whether rituximab maintenance confers a longer total duration of rituximab benefit than does rituximab retreatment. RCTs are also needed to evaluate the potential benefit of immediate vs delayed rituximab or RIT for asymptomatic, low tumour-burden, advanced-staged FL.

### Symptomatic or high tumour-burden advanced-stage FL

There is no evidence for superiority of any particular chemotherapy in terms of OS or quality of life for this group of patients.<sup>5</sup> RCTs have shown improvements in PFS but inconsistent effects on OS and significant increased toxicity when alpha interferon is given concurrently or following chemotherapy.<sup>34</sup> For these reasons, standard initial therapy for advanced-stage FL has involved conservative chemotherapy such as single-agent chlorambucil or CVP (cyclophosphamide, vincristine, prednisone). This approach recently changed due to results of 4 RCTs showing significant improvements in PFS, without excess toxicity, when rituximab is used in combination with chemotherapy.<sup>35–38</sup> **Table 2** summarizes these studies, which utilized various chemotherapy regimens including CVP (cyclophosphamide, vincristine, prednisone),<sup>35</sup> CHOP,<sup>36</sup> CHVP-IFN (cyclophosphamide, doxorubicin, teni-

poside, prednisone, interferon),<sup>37</sup> and MCP (mitoxantrone, chlorambucil, prednisone).<sup>38</sup> In 321 previously untreated FL patients, statistically superior outcomes without excess toxicity were found at median followup of 30 months for R-CVP compared to CVP in terms of overall response rate (81% vs 57%), complete response rate (41% vs 10%), and median time to progression (32 months vs 15 months), but not overall survival (89% vs 85%).<sup>35</sup> The role for maintenance or consolidation rituximab therapy remains uncertain: results of several RCTs suggest improved PFS but not OS.<sup>39–42</sup> Currently it is unknown whether the total duration of rituximab responsiveness is longer with maintenance rituximab or with rituximab retreatment at relapse for those who had long initial remissions.<sup>42</sup>

Three other treatment approaches worthy of comment include HDCT/ASCT, RIT and vaccines. Despite benefits reported from 3 European cooperative study group RCTs, the role of 1<sup>st</sup> remission HDCT/ASCT remains investigational.<sup>43–45</sup> The 3 RCTs generally followed a similar design: patients either received CHOP-like induction therapy and interferon maintenance or CHOP-like induction followed by HDCT +/- total body irradiation (TBI) and ASCT. The trials were of modest size (between 169 and 401 patients) and allowed crossover HDCT/ASCT at relapse in the control arms. With median followup times between 4 and 5 years, 1 study has shown statistical improvement in OS (86% vs 74%) while the other 2 demonstrated improved PFS (65% vs 33% and 59% vs 37%) for HDCT/ASCT over interferon. Because these studies failed to consistently show improved OS, involve a potentially toxic and expensive treatment that can be reserved for salvage therapy, and were conducted prior to the routine use of rituximab, HDCT/ASCT is not widely accepted as standard initial therapy for FL.

Two agents, I131-tositumomab and Y90 ibritumomab tiuxetan, afford “systemic” radiotherapy to widespread disease while limiting toxicities in normal tissues. Recently, the use of tositumomab in 76 previously untreated, relatively

**TABLE 2. RCTs evaluating the addition of rituximab to chemotherapy for indolent B-cell NHL**

Status (no. pts) <sup>ref</sup>	Median followup	Treatment arms	Overall response rate	Complete response rate	PFS
Relapsed (n = 128) <sup>50</sup>	18 months	FCM x 4 R-FCM x 4	58% 79%	13% 33%	32% 47%
Relapsed (n = 369) <sup>39</sup>	36 months	CHOP x 6 ± R-maintenance R-CHOP x 6 ± R-maintenance	72% 83%	18% 30%	31%* 68%*
Untreated (n = 359) <sup>37</sup>	30 months	CHVP-IFN R-CHVP-IFN	85% 94%	49% 76%	62% 78%
Untreated (n = 358) <sup>38</sup>	24 months	MCP x 8 R-MCP x 8	65% 85%	20% 42%	44% 69%
Untreated (n = 394) <sup>36</sup>	24 months	CHOP x 6 R-CHOP x 6	93% 97%	18% 21%	70% 85%
Untreated (n = 322) <sup>35</sup>	18 months	CVP x 8 R-CVP x 8	57% 81%	10% 40%	42% 75%

\* 68% for maintenance R, 31% without maintenance R.

young, low tumour-burden FL patients reported a 95% response rate, 75% complete response rate, and 5-year PFS of 59%.<sup>46</sup> Even higher PFS rates have been reported with a combination of chemotherapy and tositumomab.

Among several studies under way with these agents, the US Intergroup (SWOG S0016/CALGB 50102) is now comparing CHOP x 6 followed by tositumomab with R-CHOP x 6 in previously untreated patients with indolent NHL.

In 1992, Kwak and colleagues reported that immune responses could be induced against the surface immunoglobulin idiotype expressed by a patient's own B-cell lymphoma through idiotype (Id) vaccination.<sup>47</sup> The ability to induce such an immune response correlates with better prognosis.<sup>48,49</sup> The U.S. National Cancer Institute (NCI) and Genitope are currently conducting separate RCTs to evaluate Id vaccine therapy for FL in 1<sup>st</sup> remission.

### Recurrent FL

Therapeutic recommendations for recurrent FL are individualized, taking into account numerous factors including age, comorbidity, symptoms, desire to preserve future options, financial and/or reimbursement issues, weighing of risks vs benefits of treatment options, disease bulk, sites of involvement, transformation, prior therapy and duration of last response. Importantly, patients who have not received prior rituximab should be offered a rituximab-containing salvage chemotherapy protocol. The German

Low Grade Lymphoma Study Group demonstrated improvements in response rate, PFS and 2-year OS (75% vs 52%,  $p = 0.003$ ) for R-FCM (fludarabine, cyclophosphamide, mitoxantrone) over FCM alone for patients with relapsed indolent NHL.<sup>50</sup> An EORTC study randomized relapsed FL patients to R-CHOP or CHOP as reinduction therapy, and then randomized responding patients to maintenance rituximab or observation.<sup>39</sup> This study demonstrated superior CR with R-CHOP, and improved PFS with maintenance rituximab.

RIT with ibritumomab tiuxetan or tositumomab may be an option for those who have relapsed after at least 2 prior chemotherapy regimens and prior rituximab therapy.<sup>15</sup> Contraindications for RIT include > 25% marrow involvement, impaired bone marrow reserve and pregnancy. The most exciting data reported from uncontrolled studies of tositumomab or ibritumomab tiuxetan in multiply-relapsed FL involve patients who experienced very long-term PFS beyond 5 years. Unfortunately, the overall median response duration for all patients treated in these studies is < 1 year, and relative to rituximab, these agents are more expensive, difficult to administer and myelotoxic.

No large Phase 3 RCT evaluating HDCT/ASCT for relapsed FL has yet been reported. Available nonrandomized data show significantly longer PFS following HDCT/ASCT than does prior therapy within the same group.<sup>51</sup> The

GELA reported 5-year OS of 58% for relapsed FL patients treated with ASCT relative to 38% for concurrent controls ( $p = 0.0005$ ), and found in multivariate analysis that ASCT at 1<sup>st</sup> relapse was independently associated with OS. The only published RCT evaluating HDCT/ASCT for relapsed FL was stopped due to poor accrual after only 89 patients were randomized.<sup>53</sup> At median followup of 69 months, the 5-year PFS (55% vs 15%) and OS (70% vs 45%) rates significantly favoured HDCT/ASCT.<sup>53</sup> These results support a role for HDCT/ASCT in the management of selected, relapsed, chemosensitive FL patients. The use of rituximab prior to stem cell collection and the incorporation of RIT into the HDCT regimen may further improve the results of ASCT for FL.<sup>54,55</sup>

Another approach is the use of allogeneic (alloSCT) rather than autologous blood stem cell transplantation. The advantages of alloSCT over ASCT are a tumour-free graft and the potential immunologic "graft vs lymphoma" effect. AlloSCT seems to be associated with a lower relapse rate than ASCT for these diseases.<sup>56</sup> Indeed, even with followup beyond 5 years, the relapse rate seems to plateau at less than 20% after allogeneic bone marrow transplant (BMT). The plateau on the PFS curve strongly suggests that allogeneic BMT has the real potential to cure this disease. Unfortunately, OS rates are not better with alloSCT because of the morbidity and mortality associated with graft vs

host disease (GVHD) and regimen-related toxicity. In an IBMTR study FL patients who received alloSCT (n = 176), purged ASCT (n = 131) or unpurged ASCT (n = 597) between 1990–1999, the 5-year relapse rates were 21%, 43% and 58% and OS rates were 51%, 62% and 55%, respectively.<sup>56</sup> Before alloSCT can become more widely applicable to this group of patients, less toxic conditioning regimens and better methods of preventing GVHD are needed. Nonmyeloablative conditioning regimens prior to alloSCT — using significantly lower doses of pretransplant chemotherapy drugs and/or radiation — avoid toxicity from HDCT while still often inducing a graft vs tumour immunologic effect, but unfortunately also significant GVHD;<sup>57</sup> this approach will need to be proven superior to ASCT and myeloablative alloSCT in RCTs before it should be routinely adopted.

#### OTHER LYMPHOMA SUBTYPES

Management principles for peripheral T-cell lymphomas (PTCL) generally follow those outlined for DLBCL except that anti-CD20 antibodies like rituximab are not indicated. PTCL generally has a worse prognosis than DLBCL — with the exception of CD30+ anaplastic large T/null cell lymphomas, particularly those that express anaplastic lymphoma kinase (ALK), where the 5-year OS approaches 80% following CHOP.<sup>9</sup> NHL subtypes like Burkitt and lymphoblastic lymphomas require specific aggressive chemotherapy regimens similar to those used for acute leukemia, involving induction and consolidation phases as well as central nervous system preventive chemotherapy or radiation therapy.<sup>58,59</sup>


Indolent B-cell NHL subtypes are generally managed similar to FL, including the use of rituximab with chemotherapy.<sup>60,61</sup> Mantle cell lymphoma (MCL) and gastric mucosa-associated lymphoid tissue (MALT) lymphoma deserve special comment. Characteristics of MCL include the genetic anomaly t(11;14) with associated dysregulation of cyclin D1, male predominance, advanced stage with multiple extranodal sites (e.g. marrow, blood and intestinal tract), relative chemoresistance and median OS of 3–4 years with conven-

tional chemotherapy.<sup>9</sup> Recent studies suggest that the outcome for MCL may be improved by the incorporation of rituximab, high-dose cytarabine and myeloablative therapy with ASCT.<sup>62–64</sup> Researchers at the European MCL Network have reported a RCT showing improved overall response rate (94% vs 75%), CR (34% vs 7%) and an 8 month delay in relapse for responders with R-CHOP over CHOP.<sup>62</sup> The same group reported 3-year PFS of 60% vs 20% (p = 0.01) with high-dose cyclophosphamide/TBI + ASCT compared to interferon in patients responding to CHOP.<sup>64</sup> The Nordic Mantle Cell Lymphoma Project reported significant improvement in PFS and OS relative to historical controls after incorporating rituximab and high-dose cytarabine into a regimen of CHOP followed by BEAM/ASCT.<sup>65</sup> Large multicentre RCTs are required to better define the optimal initial management of MCL.

Gastric MALT lymphoma is the most common variety of extranodal marginal zone lymphoma (MZL). This disease must be distinguished from DLBCL of the stomach because early-stage gastric MALT lymphoma completely regresses in approximately 75% of patients following treatment for *Helicobacter pylori*, although remission may be delayed for several months.<sup>66</sup> Predictors of resistance to *H pylori* therapy include involvement of muscularis propria or regional nodes and molecular markers including t(11;18), nuclear expression of BCL-10 and NFκB.<sup>66,67</sup> Standard therapy for localized MZL including gastric MALT failing *H pylori* therapy is IFRT,<sup>68</sup> although other options including rituximab are being evaluated.

#### FUTURE DEVELOPMENTS

The promise for improved survival of lymphoma patients in the coming years is substantial, through the advent of more precise diagnostic criteria and disease staging, better clinical and molecular prognostication and increasing therapeutic options. After decades of investigation of immunologic cancer treatments, monoclonal antibodies like rituximab have finally entered the clinical arena as part of standard NHL management. We eagerly await results from Phase 3 RCTs evaluating naked and radi-

olabelled monoclonal antibodies, vaccine therapy and nonmyeloablative allogeneic stem cell transplant treatments to better define their respective roles in optimizing outcomes for people with NHL. 

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