FEATURE

Literature-based followup recommendations

PART 3: Common hematologic malignancies

Malcolm Brigden, MD, FRCP, FACP; Shahid Ahmed, MD, FRCP; David Sheridan, MD, FRCP

There has been a renaissance of targeted and other new therapeutic agents available for hematologic malignancies such that in tertiary centres, subspecialists may treat only a single disease entity. In addition, for malignancies such as multiple myeloma, there may now exist more investigational trials than available patients. However, medical oncologists and hematologists in regional or community practice still require a broad-based knowledge of therapeutic and followup options for the common hematologic malignancies.

As in the case of solid tumours described in Parts 1 and 2 of these recommendations, most existing post-treatment followup strategies for hematologic malignancies have evolved haphazardly, with no randomized data in relation to clinical or cost effectiveness, including laboratory testing and imaging modalities. However, while there is still little randomized evidence proving that the detection or treatment of early clinical relapse of hematologic malignancies may be associated with better outcomes, quality of life or survival, the situation is still quite different than for solid tumours. For each of the hematologic malignancies considered, early recognition of relapse and prompt retreatment of recurrence may be associated with an improved disease-free interval, survival or even cure.

These followup recommendations are intended to assist but not replace an individual physician’s judgment with respect to typical clinical situations. Followup care must be individually tailored based on disease type, stage and treatment received, other prognostic factors and overall health status, including possible therapy-related problems, as well as any available treatments following relapse. Because most recurrences will still actually be self-detected between scheduled visits, the followup plan provided to all cancer survivors must include education regarding possible symptoms of relapse to facilitate a proper self-care role.

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LEUKEMIA

Chronic lymphocytic leukemia (CLL)
The median survival in CLL post diagnosis varies between 1 and > 10 years according to initial stage and other prognostic features. Unfavourable cytogenetics, unmutated immunoglobulin heavy-chain (IgH) gene, cluster of differentiation 38 (CD38) or zeta chain-associated protein kinase 70 (ZAP 70) positivity along with short lymphocyte doubling time all identify patients likely to progress more rapidly. Recently, the increased availability of immunophenotype and fluorescence in situ hybridization (FISH) analyses has led to the potential stratification of therapeutic strategies in some centres for subsets of patients with poorer prognosis. Also, with longer historical followup data available, fludarabine-based chemotherapy combined with rituximab has been shown to provide a better outcome compared with traditional alkylating agents. However, since no curative therapies are currently available outside of transplant, a watchful waiting strategy is still advocated, with indications for treatment typically evolving around asymptomatic adenopathy or cytopenias.

Criteria exist for complete response, partial response, nodular partial response and minimal residual disease. Progressive disease is characterized by the presence of at least one of the following: increasing lymphadenopathy or hepatosplenomegaly; increase in lymphocyte count with a lymphocyte doubling time < 6 months; progressive cytopenias; or histologic transformation. Richter’s transformation of CLL (5% of patients) is frequently heralded by new systemic symptoms, rapidly enlarging lymphadenopathy plus elevated serum lactase dehydrogenase (LDH).

While no randomized data currently exist showing that early detection and initiation of treatment for relapsing patients are associated with better outcomes, effective therapies are available. For relapse or progression > 12 months after initial therapy, initial treatment may be repeated. For failure to respond or early relapse, other combined chemotherapies, other monoclonal antibodies, targeted therapies or high-dose therapy followed by transplantation all represent options. Thus, regular followup for the detection of progressive disease is important.

• Pre-therapy watchful waiting: conduct history and physical exam with emphasis on adenopathy and hepatosplenomegaly with complete hematology/biochemistry profile at regular intervals, depending on risk profile and anticipated disease progression. Annual chest x-ray and abdominal ultrasound...
may be performed to rule out asymptomatic adenopathy or visceral progression. A bone marrow examination is generally recommended prior to initiating therapy.

- Post definitive therapy, obtain history and physical every 3 to 6 months with emphasis on adenopathy and hepatosplenomegaly along with complete hematology/biochemistry profile.
- Consider repeat chest x-ray, abdominal ultrasound or computed tomography (CT) scans for response evaluation, especially if abnormal prior to therapy.
- Always include LDH, reticulocyte count and bilirubin with followup blood work, given the high incidence of autoimmune complications in CLL.
- Reserve bone marrow aspirate and biopsy for patients with cytopenias of uncertain cause.
- Undertake lymph node biopsy when Richter’s transformation is suspected.

### Chronic myelogenous leukemia (CML)

Previously, in the absence of transplantation, blast transformation with a terminal acute leukemia phase after 1–5 years uniformly characterized CML. However, the development of tyrosine kinase inhibitors (TKI; e.g. imatinib, dasatinib and nilotinib) has radically changed disease natural history, with an annual transformation rate < 1% after an initial progression-free interval of 3 years during therapy. Updated IRIS (International Randomized Interferon vs STI571) study data revealed a progression-free survival of 84% and an overall survival of 88% at 6 years. However, approximately 30% of patients are unable to complete an initial 3 years of therapy, with about 15% representing treatment failures and another 15%, drug intolerance. Both dasatinib and nilotinib have now been shown to provide earlier and slightly higher major molecular response rates, which should theoretically translate into lower ultimate treatment failure rates.

Definitions exist for hematologic, cytogenetic and molecular responses in relation to hematology profile data, traditional cytogenetics and real-time quantitative polymerase chain reaction testing (Q-PCR) for BCR-ABL transcript levels (Table 1). Since additional treatment options are now available for either initial failure to respond or suboptimal cytogenetic

### TABLE 1. CML response definitions

<table>
<thead>
<tr>
<th>Complete hematologic response:</th>
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<tr>
<td>Leukocytes &lt; 10 x 10^9/L with normal differential</td>
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<tr>
<td>Hemoglobin &gt; 110 g/L</td>
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<tr>
<td>Basophils &lt; 5%</td>
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<tr>
<td>Platelets &lt; 500 x 10^9/L</td>
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<tr>
<td>No signs or symptoms of disease (splenomegaly)</td>
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Cytogenetic responses:
- No response: Persistence of 100% Ph+ metaphases
- Minor response: 35–95% Ph+ metaphases
- Major response: 1–34% Ph+ metaphases
  - Corresponds to: 1 log reduction in BCR-ABL transcripts by Q-PCR
  - Complete response: 0% Ph+ metaphases
  - Corresponds roughly to: ≥ 2 log reduction in BCR-ABL transcripts by Q-PCR

Molecular responses:
- Major: 3 log reduction in BCR-ABL transcripts
- Complete: ≥ 4 log reduction in BCR-ABL transcripts

Ph+ = Philadelphia chromosome-positive
Q-PCR = quantitative polymerase chain reaction


### TABLE 2. CML milestone criteria and timelines

<table>
<thead>
<tr>
<th>Response</th>
<th>Duration of therapy</th>
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<tr>
<td>Complete hematologic response</td>
<td>3 months</td>
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<tr>
<td>Major cytogenetic response</td>
<td>6 months</td>
</tr>
<tr>
<td>Complete cytogenetic response</td>
<td>12 months</td>
</tr>
<tr>
<td>Major molecular response</td>
<td>18 months</td>
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or molecular responses, followup monitoring with attention to milestones is paramount (Figure 1, Table 2).9,11
• On commencing TKI therapy, obtain hematology profile and full chemistry including amylase, creatine kinase (CK), lipase and bilirubin with electrolytes every 2 weeks for the first month, every month for 2 months, then every 3 months or more with dose adjustments as indicated. Monitor thyroid-stimulating hormone (TSH) and glucose periodically as per individual TKI requirements.
• Patients should be weighed and monitored for signs and symptoms of fluid retention.
• Conduct Q-PCR testing for BCR-ABL transcript levels every 3 months for at least 5 years and then every 6 months, indefinitely.
• Perform bone marrow exam with cytogenetics at 12 months after treatment initiation.

**Expert perspectives**

**CML FOLLOWUP CARE**

Jeffrey H Lipton, PhD, MD, FRCP; Head, CML Study Group, and staff physician, Princess Margaret Hospital, Toronto; Professor of Medicine, University of Toronto.

The management of CML over the last decade or so has taken a change in direction that has deceptively suggested that the management of this disease has become easy. The improvement in outcome is dramatic: patients who had a median survival of 4–5 years in the pre-imatinib era now have predicted survival times of anywhere from 25–40 years. Blast crisis and death from CML are rare occurrences and the complicated side effects that occurred with allogeneic stem cell transplantation or interferon therapy have been replaced with milder ones associated with taking a pill.

However, in parallel with these therapeutic advances are the technologic developments in monitoring response, searching for cause of failure and standardizing testing. Performing these tests accurately is difficult and requires significant expertise in the laboratory that must match the clinical abilities of the treating physician. Not only must the physician be knowledgeable about how to monitor the patient, he/she must be diligent in looking for issues of patient intolerance that may result in problems with compliance, an important issue given that compliance can have a major impact on successful outcome. The laboratory must be able to generate the molecular results in a standardized manner that helps follow progress to undetectable disease or, more important, determine when the therapy is no longer effective. In Canada, we are blessed with good laboratories that are centrally standardized and soon to be completely standardized on the International Standard to the point that there is no excuse for any facility to be substandard or for any physician to send samples to a nonstandardized laboratory. The results we obtain will help monitor progress and, in some cases, help choose an alternate therapy in the uncommon event of failure, resulting from either intolerance or resistance. Second and even 3rd-generation kinase inhibitors on the market or in trial can rescue unsuccessful imatinib treatment. Dasatinib, nilotinib and more recently bosutinib, have been shown to be very effective at rescue or, in all cases, superior to imatinib as 1st-line therapy. Use of these medications in the latter scenario does not yet have approval in Canada, although they are used on a 1st-line basis in other parts of the world. Newer drugs such as omacetaxine and ponatinib are in trials and provide some hope that very resistant mutations may be successfully treated.

There are some cases, such as resistant mutations and clonal progression, that can only be identified with bone marrow cytogenetics, and hematologic toxicities that may only be salvaged with stem cell allografting. Sometimes the old way is the best way.

Physicians treating CML need to maintain vigilance, use all modalities of monitoring and be prepared to switch therapies appropriately. Experts across the country can help clinicians with smaller patient populations who do not have as much experience or comfort with some of the drugs. Although similar, the different kinase inhibitors have unique properties that are beneficial in overcoming side effects, but also require different emphases in followup. This is a marvellous time to be treating a disease based on such successful options. We should not become complacent.

**LYMPHOMA**

**Hodgkin’s lymphoma (HL)**

The survival of treated HL patients has improved substantially, with a cure rate > 80% for all stages. For limited-stage good-prognostic disease, it approaches 90%.12-14 Overall, 10–15% of patients with limited-stage disease will relapse, vs 35–40% of those with advanced-stage disease.13,14 Most recurrences occur within the first 5 years of treatment (up to 85% within 3 years); late relapses beyond 5 years represent a minority of patients. Late relapse is more common with nodular lymphocyte-predominant histology. Rebiopsy at the time of disease recurrence is crucial, since recurrence may indicate non-Hodgkin’s lymphoma (NHL). Postchemotherapy recurrence tends to occur at sites of prior bulky disease, while post-radiation therapy relapse is more common.
at new sites, especially marginal recurrences at the edge of radiation fields.14,15

Most low-stage patients who relapse after radiotherapy can be cured with subsequent chemotherap.14 With advanced disease, approximately 35–50% of those who fail initial chemotherapy may still be cured with reinduction therapy using a non-cross-resistant program or bone marrow transplantation, thus followup is important. Another reason for long-term surveillance of patients with treated HL is to detect treatment-related complications that exceed the recurrent disease death rate after 10 years.13-15 Chest pain needs to be taken seriously to exclude radiation-induced cardiovascular and coronary artery disease. Comorbid pulmonary and cardiovascular risk factors must be reduced by controlling smoking, hypertension and serum lipids. The risk for thyroid disease, including thyroid cancer, hypothyroidism or hyperthyroidism, is elevated post neck or mediastinal radiation, and yearly TSH determination is indicated.15 Therapy-resistant acute leukemias or myelodysplasia often associated with abnormal cytogenetics (chromosomes 7, 8) may occur within the first 10 years post therapy, most frequently after alkylating-agent or combined-modality treatment. Following radiation therapy, treatment-induced solid tumours, particularly breast and lung cancer, show a steady increase with no plateau for at least 20 years, and there is increased risk of malignant melanoma. Women who received mediastinal radiation before the age of 30 should begin baseline mammography by age 35. Beyond this, it is difficult to know if mammography should be performed more often than in the general population.14,15

The International Prognostic Score, a 7-parameter risk stratification index for relapse incorporating, age, sex, stage, serum albumin, hemoglobin and white cell/lymphocyte counts allows for prediction of later potential outcomes.13,14 Similarly, evolving data on negative interim or post-therapy positron emission tomography (PET) scanning have demonstrated separation into good- and poor-risk groups for relapse or poorer outcomes.13,15 However, to date there has been no potential modification of followup strategies based on these parameters. Despite regular followup schedules, more than 80–90% of recurrences are symptomatic and discovered by patients themselves. In addition, there have been no prospective randomized studies of routine followup in patients with HL or of the value of individual modalities including laboratory, x-ray, CT and PET scans.15 Both PET and CT scans have a high false-positive rate, and the cost of detecting a single asymptomatic recurrence may approach $50,000 for both HL and NHL.17,18 No studies have documented the effectiveness of screening for other late second malignancies, including treatment-related leukemias, most of which are symptomatically detected.15 European studies have suggested that an elevated erythrocyte sedimentation rate (ESR) may be a nonspecific but sensitive indicator of increased risk for later relapse.16

• Post definitive therapy, obtain history and physical with emphasis on adenopathy and hepatosplenomegaly along with complete hematology and biochemical profile (with possible ESR) every 3 months for the first 2 years, every 6 months for the next 3 years and then annually.
• Followup should include screening via complete blood count (CBC) for therapy-induced secondary malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

B-cell non-Hodgkin’s lymphoma (NHL)
The NHLs can be broadly divided into indolent or low-grade and aggressive, or intermediate and high-grade.20,22 In North America, B-cell lymphomas represent 80–85% of all NHL cases, with aggressive lymphoma approximately twice as common as indolent.20,21 With the possible exception of small subsets of patients with truly localized Stage I and II disease or younger patients who are eligible for curable allogeneic stem cell transplant, low-grade non-NHLs are largely incurable, resulting in a chronic relapsing course post therapy. For this reason, neither early detection of recurrence or upfront treatment of asymptomatic disease has been shown to make a difference in overall survival. This has generated several trials of watchful waiting vs immediate therapy.23 In the 3 prospective randomized controlled trials of immediate vs delayed intervention in low-grade NHL, there were no significant differences in overall survival or cause-specific survival, although complete remission rates were higher in the immediate treatment group in one trial. The median delay to first systemic treatment in the observation arms averaged 32–36 months.5 Histologic transformation into aggressive NHL is noted in all subtypes of low-grade NHLs, at a rate of approximately 3% per year, and does not appear to be influenced by the timing of first systemic therapy. Repeat biopsy to verify histology should be considered in all relapsing patients, 20-22 Approximately 50–60% of intermediate- and high-grade NHLs are initially curable with modern multiagent programs incorporating rituximab therapy. Relapse risk is highest during the first 3 years (the majority within the first 18 months), with elimination of more than 80% of risk after 3 years.21,22 For intermediate- and high-grade NHL, patients who relapse, up to 50% can still be longterm survivors if treated with high-dose chemotherapy followed by either autologous or allogeneic bone marrow transplant. Thus, early detection of relapse or treatment failure is important.
Several prognostic indexes that allow prediction of risk for relapse have been developed for both low-grade and aggressive NHL.\textsuperscript{20,21} Similarly, evolving data on negative interim or post-therapy PET scanning have demonstrated separation into good- and poor-risk groups for relapse or poorer outcomes.\textsuperscript{20,21} However, to date there has been no potential modification of followup strategies based on these parameters, and routine CT scanning has proven of limited value in the detection of asymptomatic or early relapse.\textsuperscript{24} There are also no prospective, randomized trials comparing various followup schedules or the predictive value of individual tests, including laboratory, x-ray, CT or PET scans.\textsuperscript{23,25} LDH has been reported to be a

**Expert perspectives**

**LYMPHOMA**

Michael Crump, MD, FRCP, Professor of Medicine, University of Toronto; Oncologist, Division of Medical Oncology and Hematology, Princess Margaret Hospital.

As outlined by Dr. Brigden and colleagues, most recurrences in aggressive lymphoma are self-detected or determined through the evaluation of new symptoms.

End-of-treatment scans to verify response are appropriate in all patients with curable lymphoma, including scans 2–3 months post combined-modality treatment, especially with a residual mass prior to radiation. Fluorodeoxyglucose (FDG) PET scanning has been incorporated into the revised response criteria for lymphomas for patients who have curable histologies. However, FDG-PET does not appear to be more accurate for detection of disease in the followup of asymptomatic patients, as demonstrated in a recently published large prospective study.\textsuperscript{1} The reported false-positive rate for end-of-treatment FDG-PET scans is variable, but ranges between 10–30%. They are not recommended for the routine followup of low- or high-grade lymphoma outside of clinical trials.

For HL patients, we do not uniformly recommend re-biopsy at recurrence, unless another diagnosis is possible or the primary diagnosis was uncertain. There is no need in patients who have primary progressive HL or who relapse in a prior site of disease. The low incidence of secondary NHL in long-term HL survivors also does not justify rebiopsy of all followup patients. An exception may be relapse more than 1 year post therapy, with nodular lymphocyte predominant histology where the risk of transformation to diffuse large B-cell lymphoma (DLBCL) is as high as 25%.

The American Cancer Society has recently recommended annual magnetic resonance imaging (MRI) in addition to mammography starting 8 years post therapy for women who have received chest irradiation including mediastinal, infraclavicular or axillary fields.\textsuperscript{2} As MRI may be insensitive for ductal carcinoma in situ, both MRI and mammography are required. However, modern radiation carries a much lower risk of secondary breast cancer vs age-matched population, the absolute risk per 10,000 persons is actually small due to the relatively low incidence of AML in the population. Patients with HL who have received extended field radiation that includes the upper abdomen should be carefully followed using current screening guidelines, including colonoscopy due to increased risk for secondary colon cancer.

Although combined modality therapy had been shown to significantly increase cardiovascular events in HL survivors beyond 10 years, it is now apparent that anthracycline chemotherapy alone also produces a statistically higher incidence of cardiac events, so risk factor counselling is warranted.\textsuperscript{5}

The followup of indolent lymphoma patients post first-line chemo-immunotherapy should be similar to that in those treated for curative intent. Asymptomatic disease progression by itself is not an indication for therapy, so the simple detection of increased nodal size on cross-section imaging does not represent a benefit. An exception may be persistence of bulky retroperitoneal adenopathy post completion of front-line chemo-immunotherapy, where evaluation after 6–12 months of maintenance therapy is warranted to exclude disease progression, or to avoid inappropriate continuation of therapy. Regular CBC monitoring in indolent lymphomas with initial marrow involvement, or post fludarabine therapy is appropriate due to the higher risk of secondary autoimmune cytopenias.

**References**

sensitive marker for the detection of preclinical relapse. Relapses are usually symptomatic between regularly scheduled followup visits and are rarely identified exclusively on the basis of routine imaging studies. In contrast to HL, relapses often occur at previously uninvolved sites. In addition, increased attention has recently focused on the potential carcinogenic risk of repetitive CT scanning. Since new sites of disease involvement are frequent, site-directed evaluation of prior disease has a low sensitivity for detecting recurrence.

- Prechemotherapy watchful waiting (indolent lymphomas): conduct history and physical exam with emphasis on adenopathy and hepatosplenomegaly, along with complete hematology/biochemistry profile at regular intervals, depending on risk profile and anticipated disease progression. In patients ever noted to have abdominal involvement, an abdominal ultrasound once yearly monitoring for retroperitoneal progression that threatens to cause renal or biliary obstruction may be considered.
- Post definitive therapy (indolent and aggressive lymphomas): obtain history and physical with emphasis on adenopathy and hepatosplenomegaly, along with complete hematology and biochemical profile with LDH every 3 months for the first 2 years, every 6 months for the next 3 years and then annually.
- Followup should include screening for therapy-induced secondary malignancies including MDS and AML via CBC. Annual breast mammogram is recommended for women 8–10 years post mediastinal radiation or at age 40, whichever occurs first.
- Post neck radiation, continue lifelong annual TSH monitoring and pay careful attention to dental health/saliva.
- While no randomized evidence exists for efficacy of followup scanning for indolent low-grade NHL, a final post-treatment whole-body CT will prove useful for comparison as a baseline reference for subsequent studies done to investigate symptoms. Also, in any patients earlier noted to have retroperitoneal disease, annual abdominal ultrasound to monitor for asymptomatic retroperitoneal progression that threatens to cause renal or biliary obstruction is reasonable. Followup CT scans may be reserved for symptomatic individuals.
- For high-grade lymphomas, based on the natural history of likely recurrence, a reasoned approach would also consist of an initial post-treatment baseline whole-body CT for subsequent comparison studies. Further CT exams should be done only as clinically appropriate to investigate symptoms.
- Long-term annual endoscopic surveillance is required in limited-stage gastric mucosa-associated lymphoid tissue (MALT) lymphoma post complete therapeutic response, as there is a 6-fold risk for gastric adenocarcinoma.
- Consider repeat biopsy to rule out transformation with rapidly progressing relapse, elevated LDH or systemic symptoms.
- Recommended immunization schedules are: annually for influenza; every 5–6 years for pneumococcus; and every 10 years for diphtheria and tetanus.

**DYSPROTEINEMIAS**

**Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM)**

The diagnostic criteria for plasma proliferative disorders are well established (Table 3).

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<th>Disorder</th>
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| **Monoclonal gammopathy of undetermined significance (MGUS)** | All 3 criteria must be met:  
• Serum monoclonal protein < 30 g/L  
• Clonal bone marrow plasma cells < 10%  
• Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia and bone lesions (CRAB symptoms)  
that can be attributed to the plasma cell proliferative disorder |
| **Smoldering multiple myeloma (SMM, also referred to as asymptomatic multiple myeloma)** | Both criteria must be met:  
• Serum monoclonal protein (IgG or IgA) ≥ 30 g/L and/or clonal bone marrow plasma cells ≥ 10%  
• Absence of end-organ damage similar to MGUS |
| **Multiple myeloma (MM)** | All 3 criteria must be met except as noted:  
• Clonal bone marrow plasma cells ≥ 10%  
• Presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma)  
• Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically, hypercalcemia, anemia, renal disease or bony lesions |
| **Waldenström’s macroglobulinemia (WM)** | IgM monoclonal gammopathy regardless of M-protein level (usually > 30 g/L) with > 10% bone marrow tibial cortex lymphoplasmocytic infiltration but no evidence of other lymphoproliferative disorder. If criteria are met but there is no evidence of organ damage or constitutional symptoms, the disease may be considered smoldering, indolent or asymptomatic. |

*Modified from Kyle RA et al. Leukemia 2010;24:1121-7.*
MGUS is also associated with increased risk of osteoporosis- and osteopenia-linked vertebral fractures, peripheral neuropathy and thromboembolic events.27,28 Because MM remains incurable, with significant associated skeletal and renal morbidity, serial monitoring has been recommended to attempt to diagnose MGUS transformation before the onset of serious complications. To date, however, no clinical trial has verified that lifelong annual followup of MGUS actually decreases renal or skeletal complications, improves quality of life or prolongs survival.28

SMM is defined as meeting the diagnostic criteria for multiple myeloma (M-protein levels > 30 g/L, marrow plasma cells > 10%) but without the presence of associated hypercalcemia, renal insufficiency, anemia or bone lesions (CRAB symptoms).25,26 Earlier trials utilizing traditional alkylating agents in SMM did not demonstrate improved outcomes, so treatment has been reserved for progressive disease with organ damage. However, clinical trials of newer agents are currently underway to reassess possible impact on progression-free and overall survival. Increasing anemia is the most reliable indicator of progression, but an abnormal MRI scan of the spine has also been shown to be a significant risk factor: SMM has significantly greater risk for progression than MGUS: 10% per year for the first 5 years, 3% per year for the next 5 and 1–2% per year for the next 10 years.26,28

• Initial workup includes history and physical, with emphasis on bone pain and hematologic symptoms.

### Expert perspectives

**DYSPROTEINEMIA FOLLOWUP CARE**

Darrell White, MD, MSc, FRCP, FACP, Associate Professor of Medicine, Program Director Internal Medicine Residency Training, Dalhousie University, hematologist, Queen Elizabeth II Health Sciences Centre.

It is now recognized that virtually all patients with multiple myeloma progress from monoclonal gammopathy of undetermined significance rather than acquire myeloma de novo.1 Whether this is also true of Waldenström’s macroglobulinemia is not known. MGUS is a relatively common condition that it is now recognized as a heterogeneous clonal disorder with varying rates of progression to symptomatic plasma cell or lymphoid malignancy.2,3 Predictors of increased risk include non-IgG monoclonal proteins, higher protein levels and altered serum free light chain ratio; increased numbers of aberrant plasma cells also predict progression. The purpose of monitoring these patients is to attempt to predict those likely to progress in hopes of avoiding complications such as renal dysfunction, bone disease and severe anemia. There have been no studies demonstrating that surveillance is beneficial, and likewise, there are no negative studies. As such it seems reasonable to suggest that patients with MGUS, especially those with higher risk features, should be monitored every 6–12 months with a measurement of monoclonal protein annually along with a CBC, calcium and creatinine level. Patients with smoldering myeloma are at an increased risk of progression and closer followup is warranted.

Treatment options for patients with MM and WM have expanded greatly in the past 2 decades. Although neither condition is curable with current standard therapies, improved population-based survival has been well documented in myeloma patients with timing corresponding to management advances such as high-dose chemotherapy with stem cell transplant and novel therapeutic agents.4,5 All patients will relapse but most will respond to treatment beyond first-line with many living for years with effective intermittent or maintenance therapy over several or more lines of therapy. Optimal followup for these patients has not been well studied. As suggested by the authors, patients should be followed routinely by a physician experienced in the treatment of relapsed MM and WM. Followup of patients in stable remission every 3–4 months with measurement of monoclonal protein and end-organ assessment is usual.

Multiple myeloma (MM) and Waldenström’s macroglobulinemia (WM)

The development of immune modulation and targeted therapies coupled with autologous transplantation has doubled median survival for MM patients to approximately 5 years, and complete response rates may now approach 50%.26,29 Regularly administered intravenous bisphosphonate therapy has significantly reduced the frequency and morbidity of skeletal complications. While some patients are currently kept on maintenance therapies indefinitely, many transition to watchful waiting after achieving a complete response or plateau phase. Progression is defined as > 25% increase in M-proteins from baseline.29 Patients experiencing progression stand a significant chance of responding to 2nd-, 3rd- or even 4th-line therapies. For these reasons, regular monitoring is important. However, to date there have been no randomized trials of followup proving benefit or examining the effectiveness of individual tests.29,29 WM typically follows a more benign course than MM, with therapy often not initiated until patients develop symptoms such as cytopenias, bulky adenopathy, organomegaly or hyperviscosity-related complaints.30 On disease progression, effective salvage therapy is available, so regular monitoring for relapse is important, although no randomized data for efficacy exist.

Patients on followup: On each visit, conduct history, physical examination and laboratory investigations as described above for SMM followup. Currently, there are no definitive standards for followup intervals for MM and WM. Most clinicians see patients at least every 2–3 months or more, depending on clinical symptomatology.

Patients on therapy: Each visit, obtain history, physical and complete hematology, biochemistry, SPEP and 24-hour urine with UPEP (if light chain proteinuria is present). Some centers prefer to follow FLC and FLC ratio — there is no randomized evidence that this is superior to SPEP.

In MM, consider annual skeletal survey. Rare patients may manifest progressive disease despite M-protein stability in serum and urine.

In WM, serum viscosity determination, partial thromboplastin time (PTT) and International Normalized Ratio (INR) are indicated as clinically appropriate.30

References