

Current Trends in the Diagnosis, Therapy and Monitoring of the Monoclonal Gammopathies

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Abstract

This paper provides an overview of developments in the diagnosis, therapy and monitoring of the monoclonal gammopathies, particularly multiple myeloma and AL amyloidosis. Consensus statements outlining diagnostic criteria for monoclonal gammopathy of undetermined significance (MGUS), myeloma and amyloidosis have been recently published. Understanding of the biology and pathogenesis of myeloma has accelerated in the last decade and provides the basis for improved prognostication and therapeutic interventions. Myeloma therapy has progressed with the introduction of autologous and allogeneic stem cell transplantation and the recent introduction of the novel agents, thalidomide, lenalidomide and bortezomib. Each of these therapeutic advances has contributed to the improved survival seen in this patient population. Similar treatment advances are occurring in AL amyloidosis. While serum and urine electrophoretic analysis remain the “gold standard” laboratory techniques for the accurate and cost-effective monitoring of the monoclonal gammopathies, new tests such as the free light chain assays have a complementary role. New guidelines for the monitoring of both myeloma and AL amyloidosis have been produced that incorporate these newer tests.

Introduction

The monoclonal gammopathies cover a spectrum of disorders characterised by the proliferation of clonal plasma cells that produce a monoclonal immunoglobulin (M-protein). Each M-protein consists of two heavy chains (γ , α , μ , δ , ϵ) and two light chains (κ or λ), although occasionally just light chains or heavy chains are secreted (and rarely none at all). A classification of the monoclonal gammopathies is given in Table 1. There has been rapid progress in our understanding of the disease biology of the monoclonal gammopathies leading to new diagnostic and prognostic information, better therapies, and the need for improved and standardised monitoring techniques. This review will focus on the plasma cell dyscrasias, in particular, monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma and systemic AL amyloidosis (in which the amyloid [A] is composed of immunoglobulin light chains [L]).

Current Diagnostic Criteria for the Plasma Cell Dyscrasias

The initial laboratory evaluation of the monoclonal gammopathies relies on serum and urine protein electrophoresis (SPEP and UPEP respectively) and, for select patients, the serum free light chain (FLC) assay. Agarose

gel electrophoresis is the usual method of screening for M-protein with immunofixation performed to confirm its presence and to determine its immunoglobulin heavy chain class and light chain type. Quantification of immunoglobulins may be performed by nephelometry, but densitometry of the M-protein is preferred. In myeloma the tumour cells inhibit the development of normal plasma cell clones so suppression of uninvolved immunoglobulins is frequently present. Electrophoresis and immunofixation of a 24-hour urine specimen should also be carried out for all patients. Collection of a 24-hour urine specimen is necessary because the mass of the M-protein provides an indirect measurement of the patient's tumour mass. Approximately 5% of myeloma is non-secretory as measured by SPEP and UPEP, but approximately two thirds of these patients have clonal free immunoglobulin light chains detectable by the FLC assay.¹ Bone marrow aspiration measures marrow involvement by clonal plasma cells, although the disease may be patchy in nature and sometimes the trephine sample provides better assessment. A radiological skeletal survey is used to assess the extent of bony involvement, with MRI and Positron Emission Tomography (PET) scans increasingly used for this purpose. The current diagnostic criteria for MGUS and myeloma, detailed in Table 2, require measurement of the bone

Table 1. Classification of the monoclonal gammopathies.

Monoclonal gammopathy of undetermined significance (MGUS)
Multiple myeloma
Symptomatic myeloma
Asymptomatic myeloma
Plasma cell leukaemia
Non-secretory myeloma
Osteosclerotic myeloma
Plasmacytoma
Solitary plasmacytoma of bone
Extramedullary plasmacytoma
Lymphoma
Waldenström's macroglobulinaemia
M-proteins associated with other lymphoproliferative disorders
AL amyloidosis
Heavy chain disease
Light chain deposition disease
Cryoglobulinaemia

Table 2. Definitions of myeloma and related monoclonal gammopathies (adapted from reference 2).

Standard name	New name	Definition
MGUS (Monoclonal gammopathy of undetermined significance)	MGUS (Monoclonal gammopathy)	• M-protein <30g/L • Bone marrow plasma cells <10% • No "CRAB"* • No B-cell lymphoproliferative disorder
Smouldering or indolent myeloma	Asymptomatic myeloma	• M-protein ≥ 30 g/L and/or • Bone marrow plasma cells $\geq 10\%$ • No "CRAB"*
Myeloma	Symptomatic myeloma	• M-protein in serum or urine • BM (clonal) plasma cells or plasmacytoma • "CRAB"*

*"CRAB" is organ dysfunction characterised by any one of:

C - calcium elevation (>2.75 mmol/L)

R - renal dysfunction (creatinine >173 μ mol/L)

A - anaemia (haemoglobin <100 g/L)

B - bone disease (lytic lesions or osteoporosis with compression fractures)

Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

marrow plasmacytosis, M-protein and the presence of end organ damage defined by the acronym "CRAB".² This mnemonic refers to organ damage caused by the malignant plasma cell proliferation or by the pathologic M-protein: C = hypercalcaemia; R = renal impairment; A = anaemia; B = bone lesions. Other evidence of organ damage may include symptomatic hyperviscosity, amyloidosis and recurrent bacterial infections (>2 episodes in 12 months). If any of the CRAB criteria are present, then the diagnosis is symptomatic

myeloma irrespective of the level of the M-protein or marrow plasmacytosis. If the bone marrow plasma cell percentage is $\geq 10\%$ or the M-protein is ≥ 30 g/L and there is no CRAB, then the diagnosis is asymptomatic myeloma. If the bone marrow plasma cell percentage is $<10\%$, the M-protein is <30 g/L and there is no CRAB, then the diagnosis is MGUS.

If the monoclonal light chain associated with a MGUS has amyloidogenic properties, it can deposit as amyloid

throughout the organs and tissues of the body. Table 3 outlines the relationship between myeloma, MGUS and systemic AL amyloidosis. Importantly, in AL amyloidosis, the plasma cell burden is usually very low so that detection of clonal light chains is critical if the diagnosis is not to be overlooked. Recent recommendations from the International Myeloma Working Group have indicated that serum and urine immunofixation electrophoresis as well as the FLC assay are required to screen for AL amyloidosis.³ A further publication from the Italian Centre for Amyloidosis confirms that immunofixation of urine cannot be omitted if AL amyloidosis is to be diagnosed in all cases.⁴

Monoclonal Gammopathy of Undetermined Significance

MGUS is a pre-malignant condition where an M-protein is produced by clonal plasma cells, but the plasma cells are not behaving in a malignant fashion. MGUS is a common finding in the elderly, of whom more than 3% over the age of 50 years have an M-protein in the serum.⁵ It can sometimes be associated with a variety of conditions such as lymphoproliferative disease, peripheral neuropathies, haematological disorders such as Gaucher's disease and acquired von Willebrand's disease, various skin diseases and osteoporosis. The risk of MGUS progressing to multiple myeloma or other lymphoproliferative disease is approximately 1% per year.⁶ Factors associated with an increased risk of progression include the concentration of M-protein, type of M-protein (IgG vs IgA or IgM), the bone marrow plasma cell percentage and the presence of an abnormal FLC ratio.⁷ MGUS usually requires no active medical therapy but, being a pre-malignant condition, requires monitoring so that intervention can occur before the onset of organ impairment. Current prognostic factors provide useful information about the risk of progression, but do little to alter management in most cases.

Multiple Myeloma

Multiple myeloma comprises approximately 1% of new cancer diagnoses. It is more common in men than women and has a median age of onset of 65 to 70 years. Its aetiology is unknown but radiation, benzene, solvent, pesticide and

insecticide exposure have all been implicated. The malignant plasma cells most commonly produce an IgG (50%), IgA (20%) or light chain only (20%) monoclonal protein.² It is a relentless disease unless treated, causing osteolytic bone lesions and fractures, hypercalcaemia, renal failure and bone marrow failure. A discussion of the biology and genetics of multiple myeloma is beyond the scope of this paper and readers are referred to recent reviews.^{8,9}

Prognosis in Myeloma

A number of prognostic factors have been defined in myeloma.¹⁰ These include: patient factors such as age, performance status (ability to perform daily activities) and albumin; factors reflecting tumour burden such as Salmon-Durie stage, beta-2 microglobulin and number of MRI-defined bone lesions; and factors reflecting tumour biology such as the plasma cell labelling index, CRP and IL-6, cytogenetic and gene expression abnormalities, LDH, and bone marrow microvessel density.

The original Salmon-Durie classification scheme was developed by correlating various clinical features of the disease with the estimated total body myeloma cell mass.¹¹ The M-protein mass, presence of hypercalcaemia, anaemia and number of lytic lesions were most strongly associated with myeloma mass, and creatinine was added to the scheme because of its known association with poor prognosis. The International Staging System based on beta-2 microglobulin and albumin has been widely applied to myeloma prognostication,¹² but while simple to apply, the lack of important markers of tumour biology such as cytogenetics may limit its utility. Recently prognostication based on genetic risk classification is gaining importance. Abnormalities detected by conventional cytogenetics (present in approximately one third of patients at diagnosis) reflect not only the detected genetic abnormality but also the proliferative capacity of the myeloma cell population. The finding of any abnormality by conventional cytogenetics has been associated with a poor outcome¹³ although particular cytogenetic abnormalities have also been associated with good (hyperdiploidy, t(11;14)) or

Table 3. Conceptual distinction between MGUS, myeloma and amyloidosis.

Plasma cell proliferation	Does the free light chain form amyloid?	Disease
Malignant	No	Multiple myeloma
Malignant	Yes	Multiple myeloma + AL amyloidosis
Non-malignant	No	MGUS*
Non-malignant	Yes	AL amyloidosis

*MGUS (Monoclonal gammopathy of undetermined significance)

poor (t(4;14), t(14;16), del(13)) prognosis.^{14,15} Fluorescent in situ hybridisation (FISH) has improved the detection rate for cytogenetic abnormalities in myeloma as the technique has no requirement for dividing cells. FISH-detected abnormalities associated with adverse prognosis include del 17p, t(4;14) and t(14;16), del 13q34 and, more recently, amplification of 1q and/or deletion of 1p.¹⁰ Similar to cytogenetics, gene expression profiling can also define high risk myeloma^{16,17} although such technology has not yet entered the routine diagnostic laboratory. The majority of these prognostic factors were developed in the era of conventional chemotherapy and they need to be revalidated in the era of novel agents such as thalidomide, lenalidomide and bortezomib.

The survival of patients with multiple myeloma has been steadily improving over the last two decades as documented in recent population based studies.¹⁸⁻²⁰ Median survival for all patients diagnosed in the last decade from one institution improved from 29.9 months to 44.8 months.¹⁸ In another study, the majority of this improvement appears to have been achieved in younger patients.²⁰ This improvement in outcome likely relates to improved therapies with autologous stem cell transplantation, the use of novel agents and better supportive care.

Myeloma Therapy

Therapy of myeloma has evolved considerably in the last decade. General management principles include maintenance of good hydration, analgesia, prompt therapy for infections and control of bone disease with appropriate orthopaedic intervention, radiotherapy and bisphosphonates. Traditional melphalan and prednisolone remained the cornerstone of myeloma therapy over many decades with numerous combination regimens being trialled but none proving superior.²¹ The advent of autologous stem cell transplantation demonstrated improved overall survival for patients transplanted as part of initial therapy.^{22,23} Two consecutive transplants (tandem autologous transplantation) has been shown to further improve survival compared to a single transplant in some but not all studies.²⁴ Currently, autologous stem cell transplantation is considered the standard of care for eligible patients (generally “younger” patients age ≤ 65 years). Allogeneic stem cell transplantation, in the form of “mini” or “non-myeloablative” transplants, is being assessed in clinical trials but remains investigational.²⁵ Recent major advances have been achieved with the introduction of thalidomide, lenalidomide and bortezomib (see below), all of which have been demonstrated in randomised controlled trials to improve the overall survival of patients with myeloma. Multiple new therapies are also in clinical trial including histone deacetylase inhibitors, heat-shock protein 90 inhibitors, cyclic depsipeptides, farnesyltransferase inhibitors and anti-

IL-6 antibodies amongst others. Myeloma clinical research is entering a new age of biologically targeted therapies which holds great promise.

Thalidomide, now known as an immunomodulatory agent, was originally developed as a sedative and anti-morning sickness agent and found to be a potent teratogen. It has multiple mechanisms of action as an anti-myeloma agent both directly against the myeloma cell and the supporting marrow micro-environment as well as on the immune system. Thalidomide has now been demonstrated in randomised controlled trials to improve overall survival in elderly patients with myeloma as part of initial therapy²⁶⁻²⁸ as well as in younger patients when used as maintenance therapy post-transplant.²⁹⁻³¹

Lenalidomide is an immunomodulatory agent derived from thalidomide with increased anti-myeloma potency and less potential to cause neuropathy, constipation and lethargy. It does, however, carry particular risks of deep venous thrombosis and neutropenia and remains a potential teratogen. Lenalidomide has been shown in randomised controlled studies to improve overall survival in patients with relapsed myeloma^{32,33} and is currently being studied as part of initial therapy.

Bortezomib belongs to a new class of therapeutic agents called “proteasome inhibitors”. By blocking the proteasome, bortezomib causes inhibition of the NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway. As myeloma cells are dependent on NFkB complex activity in the nucleus to drive certain transcription programs, inhibition of this pathway results in myeloma cell death. Bortezomib has been shown in randomised controlled studies to improve overall survival in patients with relapsed myeloma³⁴ as well as in elderly patients when used as part of initial therapy.³⁵

The availability of increasingly effective therapies has shifted the goals of treatment in myeloma. The attainment of a complete response or very good partial response is the goal of treatment in patients undergoing transplantation as this predicts improved overall survival.³⁶ Thalidomide, lenalidomide and bortezomib can also produce high response rates, particularly when used in combination with chemotherapy. Complete remission, which was rarely seen with melphalan and prednisolone, can now be achieved in upwards of 50% of patients in Phase II studies.³⁷ Randomised trials are now required to determine whether improved regimens based on these novel agents will reduce the need for tandem transplantation or, in fact, obviate the need for front-line transplantation altogether. Correspondingly, improved laboratory methods are now required to better define the depth of remission.

Myeloma Monitoring

In a malignancy such as myeloma where multiple different lines of therapy are available, accurate disease monitoring is critical: to enable prompt detection of ineffective therapy; to confirm disease responsiveness; to confirm achievement of important therapeutic milestones such as complete remission; to detect relapse before the occurrence of organ damage; and, in the setting of allogeneic transplantation, to detect low level early relapse. While SPEP and UPEP and immunoglobulin quantification remain the cornerstone of monitoring techniques, other laboratory measures are used to assess the disease response.³⁸ These include: the FLC assay; assessment of bone marrow disease on aspirate samples by morphology, flow cytometry or patient-specific quantitative PCR; or on the trephine using CD138 or light chain immunohistochemistry. Organ impairment is assessed by serial laboratory measurement of anaemia, renal impairment, hypercalcaemia and hyperviscosity, and by radiological assessment of bony disease with skeletal surveys, MRI and PET scanning.

New Response Definitions

In simple terms, the clinician is interested in whether the M-protein is undetectable or, if still present, its concentration. Recently, the International Myeloma Working Group published guidelines for the diagnosis and monitoring of monoclonal gammopathies (Table 4).³⁹ Laboratories should ensure that their report contains enough data that these responses can be easily calculated, particularly the achievement of complete and very good partial remissions. Similarly, in certain clinical situations (e.g. clinical trials, allogeneic stem cell transplantation) the accurate reporting of relapse from complete remission is vital. Every SPEP in this situation must undergo immunofixation to determine if the original M-protein has recurred. Early detection of relapse will permit donor lymphocyte infusion therapy in a setting of minimal residual disease where treatment is more likely to be effective.⁴⁰ The improved efficacy of myeloma therapies has also brought about a new category of response called stringent complete response.³⁹ In this category, patients who are in complete response are examined further by the FLC assay and bone marrow assessment for plasma cell clonality. If the FLC ratio is normal and there are no residual clonal plasma cells in the marrow (by flow cytometry or immunohistochemistry) then a stringent complete response has been achieved. Clinical trials are underway to determine whether achievement of such a stringent complete remission translates into better outcomes.

Causes of Clinician Confusion in Monitoring M-proteins

Scientific staff working in the area of protein electrophoresis should be aware of common causes of confusion to clinicians, especially to non-haematology medical staff. These include simple issues such as: the “M” in M-protein or M-band does

not refer to “IgM”; gamma globulins include IgA, IgG and IgM (not just IgG); and that the presence of an IgM M-protein should prompt investigation for lymphoproliferative disease rather than myeloma. Laboratories should take particular care with the choice of terms for reporting very small bands (e.g. ≤ 2 g/L), particularly in the post-autologous stem cell transplant setting. Reports require some comment as to the significance of the result, otherwise there is the danger that a small abnormal band labelled as “monoclonal” will be wrongly interpreted to mean relapse by a clinician who is not experienced in haematological disease. Rather than quantifying these small abnormal protein bands as a “monoclonal” protein on the quantitative SPEP report, it is preferable to describe the new band in the comment e.g. “There is a small discrete (type: e.g. IgG kappa) band, approximately (amount: e.g. 2 g/L) on a background of polyclonal and/or oligoclonal gamma globulins. Its clinical significance is uncertain”.⁴¹ Laboratories should keep a database of patients with known monoclonal gammopathies and, if possible, those patients known to have undergone autologous or allogeneic stem cell transplantation. Such databases add considerably to the efficiency and quality of laboratory reporting.

Quantification of M-proteins by nephelometry is a useful adjunct to SPEP and UPEP in monitoring patients. While the two techniques are complementary, it is important to remember that in assessing response, SPEP densitometry values should only be compared to SPEP densitometry values, and nephelometry values should only be compared to nephelometry values. Although densitometry on SPEP is the preferred method of quantifying M-proteins, there are situations where quantitative immunoglobulin values may be more reliable. These include small M-proteins in the beta region (often IgA) where the “contaminating” normal immunoglobulins are often greater in quantity than the M-protein itself. In this instance, commenting on whether the M-protein appears to be present in only trace quantities by SPEP is also helpful to the clinician. At higher IgA levels (e.g. >15 g/L), nephelometry becomes inaccurate, but nevertheless, within an individual patient the nephelometric values provide useful monitoring information. This particular issue can be dealt with by appropriate commenting in the report to indicate uncertainty of measurement.

Serum Free Light Chain Assay – a Role in Monitoring?

There is a paucity of data regarding the utility of the FLC assay in myeloma monitoring. Two approaches have been proposed based on serial assessments of either the absolute value of the involved FLC or of the difference between the involved and uninvolved FLC.⁴² In non-secretory myeloma, one small publication has reported that in six patients the FLC changes generally correlated with the patients’ clinical

Table 4. Response criteria for multiple myeloma (adapted from Durie et al. reference 39).

Response Category	Criteria
sCR	CR as defined below, plus • Normal FLC ratio, and • Absence of clonal plasma cells in the bone marrow by light chain immunohistochemistry or flow cytometry
CR	• Negative immunofixation of serum and urine, and • Disappearance of soft tissue plasmacytomas • $\leq 5\%$ bone marrow plasma cells
vgPR	• Serum or urine M-protein only detectable by immunofixation, or • $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg/day
PR	• $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg/day • If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between the involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein and FLC are unmeasurable, a $\geq 50\%$ reduction in plasma cells provided the baseline bone marrow plasma cell percentage was $\geq 30\%$ • In addition to the above listed criteria, a $\geq 50\%$ reduction in the size of any soft tissue plasmacytomas present at baseline is also required
PD	Increase of $\geq 25\%$ from baseline in any of the following: • Serum M-component (the absolute increase must be ≥ 5 g/L) • Urine M-component (the absolute increase must be ≥ 200 mg/day) • The difference between involved and uninvolved FLC levels. The absolute increase must be > 100 mg/L (only in patients without measurable serum and urine M-protein levels) • Bone marrow plasma cell percentage (the absolute % must be $\geq 10\%$) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse from CR	• Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of $\geq 5\%$ plasma cells in the bone marrow • Appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion, or hypercalcaemia)

sCR = stringent CR; CR = complete response; vgPR = very good partial response; PR = partial response; PD = progressive disease; FLC = free light chain

progress.¹ Serial bone marrow examinations are the only alternative for monitoring this subgroup of patients. In light chain myeloma there have been several studies which have documented a weak correlation between the serum FLC and 24-hour urinary Bence Jones protein (BJP) measurement at diagnosis,⁴²⁻⁴⁵ and one study showing a poor correlation between the percentage change in FLC and urinary BJP measurement after chemotherapy.⁴² Measurement of 24-hour urinary BJP has been shown to correlate with myeloma cell mass and its role in myeloma monitoring has been validated by decades of clinical trial research. As such, prospective clinical studies will be needed to demonstrate the utility of the FLC

assay in the monitoring of patients with light chain myeloma. In patients with intact immunoglobulin myeloma, serial FLC assessments do not yet have a defined role. One study has demonstrated that patients with marked early FLC reductions have worse outcomes, possibly because patients with rapidly responsive myeloma also have the most aggressive disease.⁴⁶ The FLC assay may also be useful to detect light chain escape particularly if urinary BJP analysis is neglected.⁴⁷ Another recent report of 2648 samples from 122 patients with intact immunoglobulin myeloma was unable to define a useful role for FLC monitoring in this group of patients.⁴⁸ The other role of the FLC assay in intact immunoglobulin myeloma is to

define a stringent complete response, the importance of which awaits definition.

In summary, the FLC assay appears to be a useful tool for monitoring patients with oligosecretory disease and non-secretory myeloma, and potentially in light chain myeloma, especially in those patients with renal failure where 24-hour urinary BJP measurements are not reliable.³ At present, the FLC assay should be viewed as complementing but not replacing 24-hour urinary BJP measurement.

Laboratory Techniques to Measure Minimal Residual Disease

Flow cytometry of the bone marrow plasma cell population can distinguish myelomatous plasma cells from their normal counterparts on the basis of aberrant expression of several markers (CD19, CD38, CD56 and CD45).⁴⁹⁻⁵¹ In experienced laboratories the technique has a limit of detection of 0.01% of plasma cells, and can thus be used to detect not only small amounts of minimal residual disease but also normal immune reconstitution. Approximately 40% of patients in complete remission by standard criteria can be shown to have residual malignant plasma cells by flow cytometry,⁵² and this residual disease correlates with long-term outcome.^{53, 54} Quantitative PCR strategies have also been examined in the monitoring of myeloma. Using patient specific idiotype primers, very low level disease can be detected. However, the technique is expensive, labour intensive and not applicable to all patients.^{55,56} One interesting aspect of disease monitoring that has only recently been examined relates to the changes in bone lesions as detected by MRI or PET imaging. The Arkansas group has shown that the number of MRI-detectable bone lesions independently predicts survival, and that resolution of MRI-detectable bone lesions (resolution generally delayed 41 to 58 months after complete remission in patients presenting with more than seven bone lesions) identifies a subgroup of patients with superior survival.⁵⁷ It appears that with the advent of more effective therapies, eradication of all bony myelomatous lesions will become a realistic goal of therapy and techniques to monitor this aspect of myeloma will become more important.

Systemic AL Amyloidosis

In systemic AL amyloidosis, monoclonal light chain fragments deposit as amyloid throughout the organs and tissues of the body. These amyloid deposits progressively accumulate and disrupt organ function leading to organ failure and death. The kidney, heart, nerves and liver are the most commonly affected organs.

Prognosis in AL Amyloidosis

The most important determinant of prognosis in patients

with systemic AL amyloidosis is the presence and severity of cardiac involvement. This may be assessed as a reduced left ventricular ejection fraction, thickened interventricular septal wall thickness, hypotension or the presence of cardiac failure. However, recent data have demonstrated that cardiac biomarkers are the best prognostic indicators. These include NT-ProBNP, BNP, troponin I and troponin T. A cardiac biomarker staging system combines measurement of troponin and NT-ProBNP to define three risk groups with median survivals of 26, 11 and 4 months, respectively.⁵⁸ The other important determinant of survival in AL amyloidosis is the response to therapy as measured by the FLC assay.⁵⁹ This assay has been a major advance in the field of AL amyloidosis, both in its diagnostic utility and in monitoring response to therapy. As the pathologic clonal FLC is directly responsible for the amyloid deposits, it is not surprising that the FLC response to therapy is a key determinant of outcome. In the absence of significant lowering of the FLC (by at least 50%), recovery of organ function does not occur and prolonged survival is unlikely.

Treatment of AL Amyloidosis

The optimal management strategy for patients with AL amyloidosis remains unclear. Early studies demonstrated that melphalan and prednisolone chemotherapy could improve survival in patients with AL amyloidosis although the benefit was marginal.^{60,61} High-dose melphalan and autologous stem cell transplantation is associated with impressive haematological and organ response rates as well as long-term survival, but is only applicable to a minority of patients with preserved organ function and good performance status.⁶² In other patients the transplant procedure has an extremely high transplant related mortality rate. A recent randomised controlled trial demonstrated no benefit for patients with AL amyloidosis who underwent transplantation compared to those treated with oral melphalan and dexamethasone.⁶³ Novel myeloma therapies such as thalidomide, lenalidomide and bortezomib have more side-effects in patients with AL amyloidosis, but appear in early studies to be promising agents.⁶⁴⁻⁶⁷

Monitoring AL Amyloidosis

AL amyloidosis has traditionally been very difficult to monitor as the plasma cell burden is usually very low. The development of the FLC assay has been a major advance in this regard and is probably the single most useful assay for monitoring the haematological response in this patient group. Nonetheless, the FLC assay needs to be interpreted together with the results of SPEP and UPEP as well as clonal bone marrow plasmacytosis and documentation of organ responses. The International Society of Amyloidosis has recently published consensus guidelines for the definitions of organ involvement

and monitoring of AL amyloidosis.⁶⁸ Care must be taken in interpreting the FLC assay as issues of assay performance affect its utility in monitoring much more than its diagnostic utility (see Tate et al. p 131 in this issue).

Typical monitoring during AL amyloidosis therapy includes FLC after each treatment cycle (often monthly) to document response. However, SPEP and UPEP still need to be performed to document the haematological response as well as bone marrows to confirm complete remission. Organ responses are generally assessed according to the pattern of organ involvement in each individual case. Cardiac disease should be followed by regular cardiac biomarker measurement (troponins, BNP or NT-ProBNP) and echocardiography. Renal disease is followed by measurement of 24-hour protein excretion and serum creatinine and/or creatinine clearance. The goal of therapy is to achieve at least a partial haematological response associated with evidence of organ response.^{59,69} Patients with a complete response have the best prognosis.⁷⁰⁻⁷²

Conclusion

Understanding of myeloma disease biology is progressing rapidly and is driving the development of new therapeutics that are already in the clinic. These novel treatments are far more effective than traditional chemotherapy approaches with better quality of remission, remission durations and overall survival. New laboratory methods are required to help direct and monitor such therapies but, for the time being, SPEP and UPEP remain the mainstay of myeloma monitoring. The FLC assay has become a valuable tool to monitor non-secretory, oligosecretory and probably light chain myeloma, and is essential to the management of AL amyloidosis.

Declaration

The Binding Site has supplied FLC assay kits free of charge for an amyloidosis study of which I am principal investigator.

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