The Hematology Journal

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Reprinted from The Hematology Journal (2003) 4, 379-398. doi:10.1038/sj.thj.6200312

Corrigendum: The Hematology Journal (2004) 5(3), in press. doi:1038/sj.thj.6200402

The Hematology Journal (2003) 4, 379–398

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REVIEW

Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation[1]

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These consensus guidelines have been compiled with input from the Scientific Advisors of the International Myeloma Foundation. Their production involved several steps including:

- A 3-day Scientific Advisors meeting, during which each specific area was presented and discussed (May 2002).
- Review of key literature, especially randomized study results, but also Medline, Internet, Cochrane database searches, and prior guidelines (Br J Haematol 115: 522–540, 2001).
- Feedback from patients participating in the International Myeloma Foundation, patient programs.

These guidelines encompass both the published literature and expert opinions. Recommendations based upon expert opinions are identified as such. The intent is for the guidelines to be international in scope, plus provide recommendations for both *clinical practice* and *research approaches*. 'Consensus' reflects general, although not necessarily unanimous, agreement. Details are discussed as appropriate. For convenience, the recommendations are divided into:

1. **Diagnostic criteria.**
2. **Staging and prognostic factors.**
3. **Frontline therapy.**
4. **High-dose therapy and transplant.**
5. **Maintenance therapy.**
6. **Supportive care and management of specific complications.**
7. **Novel therapies and new technologies.**

The Hematology Journal (2003) **4,** 379–398. doi:10.1038/sj.thj.6200312

Keywords: myeloma; multiple myeloma; guidelines; consensus; international myeloma foundation; management

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Received 5 May 2003; accepted 14 May 2003

Diagnostic criteria

- Up to the present time, the diagnostic criteria for multiple myeloma and related conditions have not been standardized.

- Several definitions for multiple myeloma are in general use, including the Durie/Salmon criteria,[1] the Kyle/Greipp criteria,[2,3] and several others.[4] In one comparative study, as many as 36% of patients were classified differently depending upon the system used.[5]
- It is therefore critically important to establish broadly accepted criteria.
- The International Myeloma Foundation brought together the International Working Group to develop criteria for the classification of monoclonal gammopathies. These criteria are currently being published.[6]

The following is a summary of the criteria, which are also detailed in Tables 1–8.

Multiple Myeloma (Table 1): The term multiple myeloma is considered to be synonymous with myeloma, plasma cell myeloma, active and symptomatic myeloma. The intent is to positively identify patients with active or symptomatic myeloma requiring systemic therapy. Conversely, the intent is to exclude patients with monoclonal gammopathy of undetermined significance (MGUS) (Table 2) and smoldering or indolent myeloma (Table 3). After much discussion, the review group decided to use evidence of 'myeloma-related organ dysfunction' as the defining element for the classification of multiple myeloma. In Table 1, the four major areas of dysfunction are: [C], Calcium Elevation; [R], Renal insufficiency; [A], Anemia; and [B], Bone abnormalities (Lytic or Osteopenic). This leads to the acronym CRAB, which is helpful for descriptive purposes.

It is helpful to consider the relationships between Multiple Myeloma (Table 1) as now defined, and prior criteria. Multiple myeloma as now defined is: Stages IB plus II and III A plus B in the Durie/Salmon system (Table 6), that is, Stage IA is excluded and becomes smoldering or indolent myeloma (Table 3). MGUS stays the same. A way to bring all these together is discussed as part of the new 'Durie/Salmon PLUS' staging system, which incorporates new imaging techniques (Table 7).

As in the past, it is important to emphasize that the 'myeloma-related organ dysfunction' or CRAB features must be myeloma related. This may require biopsy and/or other specialized testing.

MGUS (Table 2): The nature of MGUS is well known.[7] The criteria outlined in Table 2 are the same as those used widely in the past. Alternate acronyms were considered by the group, including MG (monoclonal gammopathy), PMG (primary monoclonal gammopathy), and UMG (unassociated monoclonal gammopathy). In the absence of a discrete molecular classification it was elected to retain the MGUS acronym. It was noted that several additional tests frequently support a diagnosis of MGUS, including a low bone marrow plasma cell labeling index (0 or $<0.2\%$) or negative Ki-67 monoclonal antibody staining. There should be no clinical or laboratory features of amyloidosis or systemic light-chain deposition disease. Whole-body FDG/PET imaging is negative in MGUS (Table 7).

Smoldering[8] *or indolent myeloma* (Table 3 *and Stage IA* (Table 6)): This intermediate category between MGUS and multiple myeloma, as now defined, is stage IA myeloma in the Durie/Salmon system (Table 6). As noted in Table 3, such patients can have mild degrees of 'myeloma-related organ dysfunction' including anemia and elevated serum creatinine. Such patients can on occasion be eligible for supportive care measures such as erythropoietin and/or bisphosphonate and/or other

Table 1 Multiple myeloma* Diagnostic criteria: all three required

1	Monoclonal plasma cells in the bone marrow $\geq 10\%$ and/or presence of a biopsy-proven plasmacytoma
2	Monoclonal protein present in the serum and/or urine[a]
3	Myeloma-related organ dysfunction (1 or more)[b]
	[C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal)
	[R] Renal insufficiency (serum creatinine > 2 mg/dl)
	[A] Anemia (hemoglobin < 10 g/dl or 2 g $<$ normal)
	[B] Lytic bone lesions or osteoporosis[c]

**Note*: These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma (Table 3).

[a]If no monoclonal protein is detected (nonsecretory disease), then $\geq 30\%$ monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

[b]A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

[c]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then $\geq 30\%$ plasma cells are required in the bone marrow.

Table 2 MGUS Diagnostic criteria: all three required

1	Serum monoclonal protein and/or urine monoclonal protein level low[a]
2	Monoclonal bone marrow plasma cells $< 10\%$
3	Normal serum calcium, hemoglobin level and serum creatinine
	No bone lesions on full skeletal X-ray survey and/or other imaging if performed
	No clinical or laboratory features of amyloidosis or light-chain deposition disease

[a]Low is defined as: Serum IgG < 3.0 g/dl; serum IgA < 2.0 g/dl; urine monoclonal kappa or lambda < 1.0 g/24 h.

Table 3 Smoldering or indolent myeloma* Diagnostic criteria: all three required

1	Monoclonal protein present in the serum and/or urine
2	Monoclonal plasma cells present in the bone marrow and/or a tissue biopsy
3	Not meeting criteria for MGUS, multiple myeloma, or solitary plasmacytoma of bone or soft tissue

**Note*: These criteria identify Stage IA myeloma by Durie/Salmon stage.

Table 4 Solitary plasmacytoma of bone Diagnostic criteria: all three required

1.	Biopsy-proven monoclonal plasmacytoma of bone in a single site only. X-rays and MRI and/or FDG PET imaging (if performed) must be negative outside the primary site. The primary lesion may be associated with a low[a] serum and/or urine M-component
2.	The bone marrow contains $< 10\%$ monoclonal plasma cells
3.	No other myeloma-related organ dysfunction

[a]Low is defined as: serum IgG < 3.5 g/dl; serum IgA < 2.0 g/dl; urine monoclonal kappa or lambda < 1.0 g/24 h.

therapies. For example, some patients with an isolated plasmacytoma fall into this category. Note was made of the fact that as for MGUS, additional testing may indicate a greater or lesser likelihood of stability. Abnormalities on MRI and/or FDG/PET imaging indicate increased risk of early disease progression.

Solitary plasmacytoma of bone (Table 4): Patients with early-stage myeloma must also be distinguished from those with an isolated or solitary plasmacytoma. Imaging must reveal only a single lesion which is a biopsy-proven plasmacytoma. Routine bone marrow biopsy is normal (<10% plasma cells) and there is no organ dysfunction. If the bone marrow contains ≥30% monoclonal plasma cells, then the diagnosis is multiple myeloma (Table 1). If the bone marrow contains ≥10% <30% monoclonal plasma cells, then the diagnosis is smoldering or indolent (Stage IA) myeloma (Table 3).

Other criteria, which do not directly impact the definition of myeloma, are published in a separate manuscript.[3] Both extramedullary plasmacytomata and plasma cell leukemia can occur as manifestations of multiple myeloma as well as independent disease states. Coexistence of extramedullary disease (EMD) and/or plasma cell leukemia with multiple myeloma confers poor risk, as noted in Table 7.

Required testing at diagnosis

Most of the recommended tests for the diagnosis of myeloma and related conditions are well established and widely accepted. Tables 4 and 5 summarizes the testing recommended as part of these guidelines. Points of emphasis and discussion were:

(a) *M-component measurement*: M-component measurement using serum protein electrophoresis (SPEP) and/or urine protein electrophoresis is preferred. However, nephelometric measurements are acceptable and for some patients, for example, with multimeric or aggregated M-component, particularly IgA in type, this can be preferred and more reproducible. At lower levels of serum M-component, nephelometry is essential. If no M-component is detected, the Freelite™ test can be utilized to measure the levels of free kappa/lambda light chains and the ratio.[9,10] This new ultra-sensitive technique for free light-chain analysis can provide a quantifiable marker in approximately 70% of patients with nonsecretory disease and/or minimal residual disease. The new serum 'Freelite' test is also positive in the majority of patients with detectable urine monoclonal protein. Although serum Freelite measurements can be used for serial monitoring, urine protein measurement for light-chain analysis is still recommended. Periodic 24-h urine collection is still required, for example, to quantify urine protein levels. The amounts of both Bence Jones light-chains and urine albumin are important. Increased levels of albumin can have several causes, including the development of systemic amyloidosis and/or light-chain deposition disease or bisphosphonate toxicity.

Table 5 Required testing for possible myeloma

History and physical examination
Complete blood count with differential and peripheral blood smear review
Chemistry panel including calcium and creatinine
SPEP, immunofixation
Nephelometric quantitation of immunoglobulins
Routine urinalysis, 24 h urine collection for electrophoresis and immunofixation. Quantification of both urine M-component level and albuminuria
Bone marrow aspirate and trephine biopsy (cytogenetics, immunophenotyping, and plasma cell labeling index, if available)
Bone survey including spine, pelvis, skull, humeri, and femurs. MRI of the axial skeleton is very informative if available/feasible but is not required. Whole-body FDG/PET imaging is also not required, but can be used to confirm MGUS or exclude unsuspected and/or extramedullary myeloma, infection, and/or an associated second malignancy
β_2-microglobulin, C-reactive protein, and lactate dehydrogenase
Measurement of free monoclonal light chains is an option if conventional M-component quantitation is negative or equivocal

(b) *Diagnostic Imaging*: Standard radiologic skeletal survey is the 'gold standard' for baseline evaluation.[11] Targeted X-ray of specific areas (eg, rib series) can be additionally helpful.

Computed tomography can be helpful for the evaluation of localized areas of concern.[12] Areas of critical bone destruction can be clearly delineated to facilitate radiation therapy and/or surgical intervention.

Magnetic resonance imaging (MRI) with T1/T2 settings plus STIR sequences and use of gadolinium for enhancement is now widely used.[13] MRI is helpful in assessing the bulk of disease as well as a variety of clinical problems including bone pain, cord compression, osteopenia, or uncertain staging. In patients with multiple myeloma, the number and size of lesions on MRI correlate with prognosis. In patients with asymptomatic or smoldering myeloma, MRI findings correlate with likelihood of transition to multiple myeloma (see Staging and prognostic factors).

Whole-body FDG/PET imaging can be useful in clarifying disease classification (eg, completely negative in MGUS) or prognostic category (eg, demonstration of EMD and/or assessment of elevated LDH).[15] With wider use, it may become a recommended technology. FDG/PET imaging can substitute for MRI if this is not performed or not available for staging, restaging, and/or serial monitoring.

Summary assessment of imaging:

There have been major advances in imaging technology in recent years.

Although the new technologies are not mandated, the benefits of anatomic and functional staging with MRI and FDG/PET where and/or when available cannot be overemphasized. Staging and treatment can potentially change in 15–25% of patients. This leads to consideration of new staging systems as discussed below.

(c) *Cytogenetic and molecular analysis*: There was considerable discussion about the role of cytogenetic and molecular studies for routine prognostic classification. Numerous correlations exist between chromosome

abnormalities and prognosis or different patterns of disease. Chromosome 13 deletion is widely recognized as a poor prognostic factor.[16,17] However, there is no unanimity or consensus as to whether or not cytogenetic testing is a mandatory baseline procedure. This is both because standardized bone marrow cytogenetic testing is not universally available and because selective management of patients with chromosome 13 deletions and/or other abnormalities is not clearly delineated. No specific alternate therapy is routinely recommended for patients with abnormal chromosomes. Further details are discussed under relapsing disease, research approaches, and clinical trials.

Summary assessment of genetics:

Baseline cytogenetic studies are recommended as a routine in clinical trials, whenever feasible. In clinical practice, availability of cytogenetic information is also helpful to guide potential treatment selection and future trial eligibility.

It is likely that a new molecular classification for plasma cell disorders will be feasible in the near future. The precise molecular markers and the technologies required for testing remain to be determined.

Staging and prognostic factors

The Durie/Salmon staging system[18] is widely used (Table 6).

Table 6 Durie and Salmon staging system

CRITERIA
Stage I (low cell mass)
All of the following:
Hemoglobin value >10 g/dl
Serum calcium value normal or <10.5 mg/dl
Bone X-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only
Low M-component production rates
IgG value <5.0 g/dl
IgA value <3.0 g/dl
Urine light-chain M-component on electrophoresis <4 g/24 h
Stage II (intermediate cell mass)
Fitting neither Stage I nor Stage III
Stage III (high cell mass)
One or more of the following:
Hemoglobin value <8.5 g/dl
Serum calcium value >12 mg/dl
Advanced lytic bone lesions (scale 3)
High M-component production rates
IgG value >7.0 g/dl
IgA value >5.0 g/dl
Urine light-chain M-component on electrophoresis >12 g/24 h
Subclassification (either A or B)
A: relatively normal renal function (serum creatinine value) <2.0 mg/dl
B: abnormal renal function (serum creatinine value) ≥2.0 mg/dl
Examples
Stage IA (low cell mass with normal renal function)
Stage IIIB (high cell mass with abnormal renal function)

New imaging technologies such as MRI and FDG/PET have made anatomic and functional staging much more precise.[15,19] It is possible to integrate these new technologies into the Durie/Salmon system[19] to create, for example, the Durie/Salmon PLUS system (Table 7). This new system includes MRI and/or FDG/PET imaging plus risk factors in addition to serum creatinine (<2 mg/dl; >2 mg/DL) to subclassify as A or B.

Several staging and prognostic factor systems have been evaluated to identify a simple prognostic classification system. A reappraisal in 1986 identified serum β_2-microglobulin and serum albumin as a useful combination for survival prediction (20). The South West Oncology Group (SWOG) recently developed a new staging system (Table 8) using these two parameters.[21]

Several groups have attempted to incorporate genetic information into a new prognostic system.[16,17] The French (IFM) group used chromosome 13 deletion by (fluorescent *in situ* hybridization) (FISH) combined with serum β_2-microglobulin to create a new system.[17]

New International Prognostic Index (IPI). Under the auspices of the International Myeloma Foundation (IMF), data were gathered on 11 179 patients from 17 institutions around the world, including the US, Europe and Asia.[22] The prognoses for patients receiving both

Table 7 Durie/Salmon PLUS staging system[a]

Classification	*PLUS*	*New imaging: MRI and/or FDG PET*
MGUS (Table 2)		All negative
Stage IA* (smoldering or indolent) (Table 3)		Can have single plasmacytoma and/or limited disease on imaging
Multiple myeloma Stages IB*, IIA/B*, IIIA/B* (Table 1)		
Stage I B*		<5 focal lesions; mild diffuse disease
Stage II A/B*		5–20 focal lesions; moderate diffuse disease
Stage III A/B*		>20 focal lesions; severe diffuse disease
	*A Serum creatinine <2.0 mg/dl[b] No extramedullary disease (EMD) *B Serum creatinine >2.0 mg/dl[b] Extramedullary disease (EMD)	

[a]See: 1. Bauer et al. Magnetic resonance imaging as a supplement for the clinical staging system of Durie and Salmon? *Cancer* 2002; **95:** 1334–1345.
2. Durie et al. Whole-body F-FDG PET identifies high-risk myeloma. *J Nucl Med* 2002; **43:** 1457–1463.
3. Greipp et al. Development of an International Prognostic Index (IPI) for myeloma: Report of the International Myeloma Working Group. *Haematol J* 2003; **4** (Suppl 1): P7.1 542–544.
[b]If there is a need to maximize identification of poor risk in subcategory B, additional parameters are platelets <130000/mm^3, and/or LDH above normal.[3]

Table 8A Serum β_2-microglobulin (β_2m) and serum albumin (S. Alb) staging

SWOG staging system[a]
Stage I
β_2M <2.5 mg/dl
Stage II
β_2M ≥2.5<5.5 mg/dl
Stage III
β_2M ≥5.5 mg/dl
S. Alb ≥3.0 g/dl
Stage IV
β_2M ≥5.5 mg/dl
S. Alb <3.0 g/dl

[a]Jacobson J et al. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. *Br J Haematol* 2003; **122:** 441–450.

Table 8B International Myeloma Working Group staging system

Proposed IPI[b] *staging system*
Stage I
β_2M<3.5; S. Alb<3.5
Stage II
β_2M<3.5; S. Alb>3.5
or
β_2M 3.5–5.5
Stage III
β_2M >5.5

[b]Greipp PR et al. Development of an International Prognostic Index (IPI) for myeloma: Report of the International Myeloma Working Group. *Haematol J* 2003; **4** (Suppl 1): P7.1 S42–S45.

Table 9 Recognized prognostic factors

Factor	*Significance*
Clinical	
Age	Younger – better
Performance status	Low levels – poor
Routine laboratory testing	
β_2-microglobulin	Higher – poor
Serum albumin	Lower – poor
Serum creatinine	Elevated – poor
LDH level	Elevated – poor
C-reactive protein	Elevated – poor
Hemoglobin	Low – poor
Platelet count	Low – poor
Specialized tests	
Plasma cell labeling index	High – poor
Plasma cell morphology	Plasmablastic – poor
Bone marrow cytogenetics	
Standard cytogenetics	Hypodiploidy/deletion 13 – poor
FISH analysis (chromosome 13)	13 deletion – poor
Microarray techniques	Differential patterns
Whole-body FDG/PET scan	Extramedullary – disease poor

conventional-dose and high-dose therapy (HDT) are being assessed. The most promising IPI staging system is a combination of serum β_2-microglobulin and serum albumin very similar to the SWOG system (Table 8A). The general range of prognostic factors being considered is listed in Table 9.

The IPI group is also identifying patients with particularly poor (median survival 12–24 months) versus very good survival (median survival >5 years). Risk factors associated with poor survival are elevated serum creatinine, low platelet count, poor performance status, age >65 years, and elevated LDH values if available. Conversely, survival of >5 years is associated with absence of these factors, as well as absence of chromosome 13 deletion by cytogenetic analysis and/or absence of complex chromosome abnormalities.[22]

Recommendations

- Use of the Durie/Salmon staging system is still valid (Table 6). However, if additional imaging is performed, the Durie/Salmon PLUS system can be considered (Table 7) for more precise anatomic/functional staging.
- The IPI system incorporating serum β_2-microglobulin and serum albumin (Table 8B) is now being introduced and can be considered as a new or alternate option, especially for multi-institutional study analyses.
- Additional risk group classification can be helpful, especially if new therapies are being considered or evaluated. Age is particularly important, as well as elevated serum creatinine and/or LDH, and low platelet count.
- Cytogenetic and molecular data can hopefully be used in the future for more precise staging and prognostic classification.

Frontline therapy: management of symptomatic multiple myeloma

Exclusion of patients with MGUS and smoldering/indolent myeloma: The first consideration is to identify the subset of patients with asymptomatic or minimally symptomatic disease who can receive supportive care measures alone as a first approach. Note is made of the fact that randomized studies[23,24] have failed to demonstrate any added benefit with immediate systemic chemotherapy (with, for example, melphalan/prednisone), in patients with what has been called smoldering (now asymptomatic) myeloma. Therefore, use of erythropoietin and/or bisphosphonates can be considered. However, it is also noted that the ASCO guidelines on bisphosphonate use[25] do not recommend routine use in this setting.

Conventional therapy for multiple myeloma: overview

Melphalan was first used as treatment for multiple myeloma in 1958.[26] Intermittent high-dose prednisone was subsequently shown to be effective in patients with myeloma refractory to alkylating agents in 1967.[27] In 1969, a study of 183 patients not previously treated with an alkylating agent produced a response rate of 70% for evaluable patients with 'pulse' or intermittent melphalan

(M) plus prednisone (P) versus 35% receiving intermittent melphalan alone or daily melphalan 19%.[28] Six of 14 patients (43%) unresponsive to daily melphalan and 3/15 (20%) unresponsive to intermittent melphalan responded to the intermittent M/P combination. Prednisone therefore enhanced melphalan efficacy. The median survivals in this study ranged from 11 to 35 months with a median of approximately 24 months in the intermittent M/P arm. These studies set the stage for use of MP as a frontline therapy for multiple myeloma.

In the 30 years since these investigations, numerous alkylating agent combination studies have been performed. In 1998, the Myeloma Trialists' Collaborative Group evaluated 6633 patients from 27 randomized trials comparing combination chemotherapy with melphalan plus prednisone.[29] Although the median overall response rate was 60% for the various combination schedules versus 53.2% for M/P ($P<0.00001$), there were no significant differences in overall survival. The median survival for both groups was 29 months.

These meta-analysis results are consistent with both large center and cooperative group trials during the same time frame. For example, in the SWOG, the median survivals over many protocols have remained similar at approximately 33–34 months.[19]

Response has proved to be particularly difficult to evaluate and compare between studies. In general, the $\geq$50% reduction in monoclonal protein level cutoff combined with other laboratory and clinical evidence of response has served as the indicator of 'response'. Response duration is the most consistent indicator of subsequent survival.[30]

In recent SWOG analyses evaluating all types of conventional chemotherapy, time to progression was the most reliable indicator of treatment benefit and overall survival.[30] Higher levels of response (eg, >75% regression; complete response or 'true complete response') do not in themselves predict better survival. If a particular level of response is sustained for >6–12 months, there is a trend towards better survival proportional to the magnitude of regression. This 6–12 month 'guarantee time' must be considered in evaluating treatment outcome.[31]

Summary assessment

- Despite wide variations in response rates, all conventional therapies used thus far have produced equivalent survival outcome.[29]
- The utility of a particular therapy in preparation for stem cell harvesting and transplantation is now a critical consideration.
- The major determinants of outcome with conventional therapies are the stage and intrinsic biology of the myeloma in individual patients at the start of treatment.
- The tolerance and toxicities with different therapies have become especially important in treatment decision-making.
- The time needed to achieve remission and associated side effects are also very important considerations.

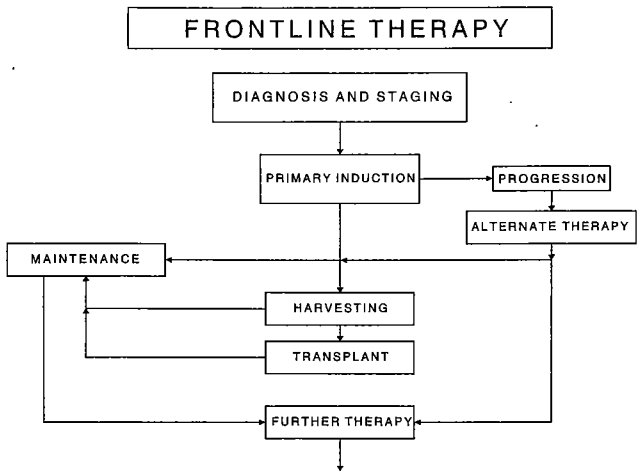

Figure 1 Outline for approaches to frontline therapy for myeloma.

Initial chemotherapy for multiple myeloma

- The general approach to frontline therapy is summarized in Figure 1.
- The frontline therapy recommendations for myeloma are currently in a state of flux (32). Many widely used therapies have little or no randomized trial support. Several new therapies have no long-term follow-up data available.
- There are six major options. The pros and cons of each are summarized in Table 10. The following reflects discussions and assessments of published data.

Melphalan (Alkeran) plus prednisone

As summarized above, melphalan, and then melphalan plus prednisone have been used since the 1960s.[33] There are only limited data to support the addition of prednisone to melphalan (Alkeran).[28] Cyclophosphomide (Cytoxan) was used for the initial comparison of an alkylating agent versus controls.[34] Cytoxan versus melphalan gave equivalent results in two UK MRC studies.[35,36] Different dosages and schedules of alkylating agents have been used over the years. This makes it difficult to compare relative efficacies.[29] Melphalan has tended to be preferred because of tolerance in an elderly myeloma population. Melphalan plus prednisone has not been directly compared to melphalan plus dexamethasone. More complex combinations of standard agents have proven overall to give equivalent results to melphalan and/or prednisone.[29] Some possible exceptions involving ABCM (UK/MRC protocol)[37] and the M2 protocol (Sloan Kettering) and ECOG protocols[38] are discussed below:

Recommendations

- Melphalan/prednisone remains a valid option, especially for elderly patients.

- Melphalan is not recommended if stem cell harvesting is planned.

Cytoxan with or without prednisone Although less popular, Cytoxan is a valid option alone or with prednisone, as is melphalan.

Use of Cytoxan has the advantage that it produces less stem cell injury than melphalan.

Cytoxan can be used with or after VAD or dexamethasone, especially if response has not been achieved. CVAD or 'hyper-CVAD' has been used by some groups,[39] especially in high-risk settings, such as plasma cell leukemia or in patients with poor risk features (eg, EMD and/or elevated LDH).

More complex alkylating agent combinations Several combinations are widely used.[29]

In the UK, the ABCM regime is often preferred because of superiority over melphalan in the MRC study. However, in a crosstrial comparison, ABCM and VMCP/VBAP produced equivalent results.[40] Since, as discussed below, VMCP/VBAP produces only questionable benefit over MP, the added benefit of complex combinations is tenuous at best.

In the US, the VMCP/VBAP protocol is sometimes used because of superiority in a SWOG study. However, a later, large Italian study failed to show added benefit.

In the US, the M2 protocol (VBCMP) is also sometimes preferred because of survival superiority shown in an ECOG study.[38]

Overall recommendations

- Combinations provide little added benefit.
- Combinations result in added toxicity, inconvenience, and expense.
- Combinations will typically preclude or impair subsequent stem cell harvesting.

VAD

Since VAD was first introduced,[41] it has become the most widely used choice for frontline therapy.

A main reason for the widespread use is the 60–70% response rate. The primary goal is to achieve the maximum response in the largest percentage of patients as rapidly as possible as a basis for early harvesting and transplant. With the increased popularity of stem cell transplantation, VAD became an ideal initial cytoreduction strategy prior to stem cell harvest.

However, in recent years the popularity has been substantially tempered by the inconvenience, toxicity, and potential for medical complications.

The need for a central catheter and 4-day infusion is inconvenient, expensive, and can lead to complications such as infection and coagulation problems. Vincristine adds potential neurotoxicity without major added benefit. The Adriamycin infusion adds hair loss and potential cardiotoxicity with perhaps only 10–15% additional benefit in terms of likelihood of response.

Table 10 Frontline therapy options

Options	*Comments*
Melphalan/ prednisone	Still an option, especially for elderly patients
Cytoxan alone or in combination	Can be useful alone or in combination with less stem cell injury than melphalan
Alkylating agent combinations	Really only an option if stem cell transplant is not planned
VAD regimen	Still a major frontline approach; can have significant disadvantages
Dexamethasone or other steroids alone	A valid option, especially with renal insufficiency and/or reduced blood count values
Thalidomide plus dexamethasone	A new oral option worthy of consideration but without a long track record

Since the exact magnitude of response does not critically impact either the ability to harvest or the ultimate outcome from subsequent HDT, the role of Adriamycin has come into question. Alternatives to Adriamycin include Doxil®, idarubicin, and mitoxantrone (see Table 10).

Recommendations

- VAD is an acceptable and well-studied frontline option.
- However, the disadvantages outlined above are significant.
- Several variations on VAD are in use and are also acceptable alternatives (see Table 11).
- It is valid to consider other options as discussed below.

Pulse dexamethasone alone

Although pulse dexamethasone is widely used both at relapse as well as frontline, limited trial data are available.[42,43]

Using the 40 mg/day (or 20 mg/m^2/day), 4-day on, 4-day off schedule, the upfront response rate is high: 40–50% or perhaps higher. Therapy can be intensified and/or changed as necessary to achieve response sufficient for harvesting or clinical remission.

This level of response is acceptable as a first approach.

The toxicity with intensive pulse dexamethasone is the primary concern. Limiting toxicities range from dramatic mood swings, loss of sleep, irritability and/or acute attention deficits, to fluid and weight retention, secondary diabetes mellitus, gastro/esophageal problems, infection susceptibility, proximal muscle weakness, visual impairments including cataracts, and skin/blood vessel fragility enhancement.

Less intensive and alternate steroid (eg, prednisone or methyl-prednisolone)[43] schedules are used by many physicians, but without major support from randomized clinical trial data (see Table 10). Nonetheless, results with VAD and VAMP are equivalent. Methyl-prednisolone appears to have lesser toxicity.

Provided sufficient response occurs, there is no difference either in stem cell collection or engraftment after pulse dexamethasone alone versus VAD.

Recommendations

- Pulse dexamethasone (or equivalent steroid therapy) alone is an acceptable primary induction for newly diagnosed myeloma.
- Dose reduction/modifications may be required because of toxicities. The impact of dose, drug, and/or schedule modifications upon outcomes are not known. The standard dosages and potential modifications are summarized in Table 10.

Thalidomide plus dexamethasone

The details of thalidomide therapy are summarized under relapse management.[44–46]

Owing to success in the relapse setting, several groups have introduced thalidomide in a frontline setting.[47,48] A Mayo Clinic study combining pulse dexamethasone with thalidomide produced a response rate of 64%. This is a response sufficient to proceed with stem cell harvesting. Since this is very similar to that achievable with VAD, and because of the disadvantages of VAD summarized above, the thalidomide/dexamethasone combination has rapidly emerged as an acceptable frontline option. Many studies are ongoing. No large trial data sets are available. Several issues are unresolved, including thalidomide dose, dexamethasone dose and schedule, and concomitant supportive care/treatment/medications, such as prophylactic anticoagulation. Currently, 200 mg of thalidomide a day is recommended, although lower doses such as 50–100 mg may be equally effective and less toxic (Tables 12 and 13).

Recommendations

- Thalidomide/dexamethasone can be considered as a frontline treatment option.
- Since the Mayo Clinic study incorporated stem cell harvesting and subsequent HDT, this is a reasonable treatment setting for prior thalidomide/dexamethasone.
- However, much more data and follow-up are required to answer many questions about efficacy, toxicity, time to first progression, and overall outcome.
- Outside of clinical trials, thalidomide is only available through the STEPS. (Celgene) program or a similar monitoring procedure depending on the country and source(s) of drug. (e.g. Pharmion: UK/Europe).

Table 11 VAD and similar alternate regimens

Regimen	*Drugs*
VAD	Vincristine 0.4 mg/day 24 h infusion, days 1–4 Doxorubicin (Adriamycin) 9 mg/m²/day 24 h infusion, days 1–4[a] Dexamethasone 40 mg/day i.v./p.o., days 1–4, 9–12, 17–20 (35-day cycle)
VAMP	Vincristine 0.4 mg/day 24 h infusion, days 1–4 Doxorubicin 9 mg/m²/day 24 h infusion, days 1–4 Methylprednisolone 1 g i.v./p.o., days 1–5
C-VAMP	Cyclophosphamide 500 mg i.v., days 1,8,15 Vincristine 0.4 mg/day 24 h infusion, days 1–4 Doxorubicin 9 mg/m²/day 24 h infusion, days 1–4 Methylprednisolone 1 g i.v./p.o., days 1–5
DVD	Liposomal doxorubicin (DOXIL™) 40 mg/m² i.v., day 1 Vincristine 2 mg i.v., day 1 Dexamethasone 40 mg/day i.v./p.o., days 1–4
Z-Dex	Idarubicin (Zavedos) 10 mg/m²/day p.o., days 1–4 Dexamethasone 40 mg/day i.v./p.o., days 1–4
MOD	Mitoxantrone 9 mg/m²/day 24 h infusion, days 1–4 Vincristine (Oncovin) 0.4 mg/day 24 h infusion, days 1-4 Dexamethasone 40 mg/day i.v./p.o., days 1–4, 9–12, 17–20 (35-day cycle)

Segeren CM et al. *Br J Haematol* 1999; **105:** 127–130.
[a]An alternate regimen with equivalent efficacy gives the Doxorubicin (Adriamycin) as 9 mg/m² each day for 4 days by rapid i.v. infusion.

Table 12 Steroid dosages and schedules

Steroid	*Dosage*	*Schedules*
Dexamethasone (Decadron®)	40 mg or 20 mg/m² (see Table 10)	4-day oral pulse repeated q 4–10 days, reduced to q month or less frequent as maintenance
	Often reduced to 20–10 mg range because of toxicity	1 day oral pulse q week also used for maintenance
Methylprednisolone (Medrol®)	213 mg of Medrol equivalent to 40 mg Decadron	5-day i.v. pulse as part of VAMP
	The usual dose is 1 g i.v. (eg, for VAMP (Table 10)	1-day i.v. pulse q week or less often as maintenance
	Oral schedules of 64 mg q.o.d. and 96 mg p.o. q week are also used.	Oral maintenance q.o.d. or weekly
Prednisone	270 mg prednisone is equivalent to 40 mg of Decadron However, typical dose of prednisone is 60 mg/m² or 100 mg	4- or 5-day oral pulses with MP/VMCP/VBAP, etc. 50 mg p.o. three times/week is typical maintenance; dosage reduction often required

Management when frontline therapy fails to produce an adequate response

WITH A PLAN TO PROCEED TO STEM CELL TRANSPLANT:

Proceed directly with transplant: Provided acute clinical problems have been resolved, it is usually possible to proceed with stem cell harvesting and transplant even if < 50% regression has been achieved.[49] Fortunately, the percentage of regression pretransplant does not predict for the outcome post-transplant.

Alternate therapy pre-harvesting and transplant: If it is felt that additional cytoreduction is required before proceeding to harvest stem cells, there are several options:[50]

First therapy*	Secondary options*
DEX alone	VAD
Full VAD	i.v. Cytoxan alone or with VAD (CVAD or 'hyper' CVAD)
Cytoxan	DEX or full VAD
Any of the above	Thalidomide/DEX or BLT-D (three drug: Biaxin/low dose thalidomide/DEX protocol)
Any of the above	EDAP, DCEP, or DT-PACE

The details of the DCEP, DT-PACE, and BLT-D regimens are summarized in Table 13.

Harvesting: High-dose Cytoxan alone or with VP-16 (etoposide) plus G- or GM-CSF is typically used for stem cell harvesting. Thus, some degree of cytoreduction is frequently part of the harvesting process.

WHEN THERE IS NO PLAN FOR STEM CELL HARVESTING OR TRANSPLANT:

In this situation, the main difference is that melphalan plus prednisone can be an option if VAD and/or dexamethasone have failed. Also, intravenous (i.v.) melphalan in attenuated doses, $<100\,mg/m^2$, can be considered. Melphalan-containing combinations such as ABCM and the M2 protocol are also potential options.

The other options listed above can also be considered.

WHEN THERE IS PERSISTENT PRIMARY RESISTANT OR PROGRESSIVE DISEASE:

If standard options listed above have failed, and/or are not feasible or selected for some reason, research options are available. Clinical trials are discussed later.

Table 13 Relapse regimens

DCEP[a]
- Dexamethasone 40 mg/day p.o., days 1–4
- Cytoxan (cyclophosphamide) 750 mg/day, days 1–4 (CI)
- Etoposide (VP-16) 75 mg/day, days 1–4 (CI)
- Platinol (cisplatinum) 25 mg/day, days 1–4 (CI)
- CI = continuous intravenous infusion
- G-CSF 300 μg/day until granulocyte recovery

DT-PACE[b]
- Dexamethasone 40 mg/day p.o., days 1–4
- Thalidomide 400 mg/day p.o., ongoing daily
- Platinol (cisplatinum) 10 mg/m^2/day, days 1–4 (CI)
- Adriamycin 10 mg/m^2/day, days 1–4 (CI)
- Cytoxan (cyclophosphamide) 400 mg/m^2/day, days 1–4 (CI)
- Etoposide (VP-16) 40 mg/m^2/day, days 1–4 (CI)
- CI = continuous intravenous infusion
- G-CSF 300 μg/day until granulocyte recovery

BLT-D (modified)
- Biaxin (clarithromycin) 500 mg(*XR*)/day p.o. or 250 mg/day b.i.d.
- Low-Dose thalidomide 50 mg h.s./day p.o.
- Dexamethasone 40 mg/day p.o. q.d., 4 days, then 40 mg p.o. q.d. for 1 day/week

XR = extended release

Dose adjustments are as follows: biaxin, reduce to 250 mg q.d. or 500 mg q.d. every other week if necessary; thalidomide, increase daily (h.s.) dose to a maximum of 200 mg q.d. if necessary to achieve response; dexamethasone, additional 4-day pulses of dexamethasone used as needed to achieve response. Dexamethasone dose reduced as necessary for tolerance (eg, 20–40 mg/day range).

Durie BGM. *Haematol J* 2003; **4** (suppl 1): 327, S234.

[a]Munshi NC et al. *Blood* 1996; **88** (Suppl.): 586a, Abstract No. 2331.

[b]Munshi NC et al. *Blood* 1999; **94** (Suppl.): 123a, Abstract No. 540.

HDT with stem cell transplantation

- The role of autologous transplantation has been extensively reviewed.[51–55]
- HDT with autologous stem cell transplantation has been shown to improve both response rates and survival in patients with myeloma. However, this approach is not curative: >90% of patients relapse.
- Complete remission (CR) rates with HDT as a planned part of front line therapy range from 24–75%.
- Partial remission (PR) rates (i.e., ≥PR) with HDT as frontline range from 75 to 90%.
- Time to progression (first progression or relapse) is 18–24 months.
- Median overall survival with HDT is in the 4–5 year range. This is reflected as being statistically superior in the randomized Attal *et al*[52] study and in, for example, the historical case-controlled Nordic Myeloma Study (2000).[56] The 'MRC Myeloma VII Trial of standard versus intensive treatment in patients aged <65 years'[53] indicated improved outcome overall with HDT, especially for patients with high serum β_2-microglobulin (in this study >8.0 mg/dl: NEJM, 2003; **348:** 1875–1883).
- Morbidity and mortality: With current growth factor, antibiotic, and other supportive care, the procedure-related mortality with HDT is very low: ca. 1%. The majority of centers use i.v. high-dose melphalan alone at a dose of 200 mg/m^2 as the preparative regimen. Since the use of TBI adds toxicity without clear survival benefit, few centers recommend TBI as part of the preparative regimen.
- Both quality of life and cost–utility analyses have been conducted for HDT compared to standard-dose chemotherapy. The Nordic Myeloma Study showed both improved quality and length (median survival of 62 months versus 44) of survival at an estimated added cost of $ (U.S.) 27 000/year.

Overall recommendations for autologous HDT

HDT with autologous stem cell support should be considered as part of the frontline therapy for newly diagnosed patients with symptomatic myeloma:

(a) The standard conditioning regimen is melphalan 200 mg/m^2. TBI is not recommended.
(b) Stem cell purging is not recommended because of added expense without additional clinical benefit.
(c) Peripheral blood stem cells are recommended over bone marrow both because of ease of collection and more rapid engraftment.
(d) The pretransplant regimens including VAD, dexamethasone, thalidomide/dexamethasone, and Cytoxan are discussed under front line therapy management of symptomatic multiple myeloma above.

Several factors influence the choice of HDT with autologous transplant

(a) Patient age[57] – Patients up to the age of 70 years can be considered, provided performance status and other parameters are satisfactory. For patients aged 60–70 years, data indicate a definite survival advantage. For patients older than 70 years, although transplant can be feasible, there are no clear data to indicate the degree of benefit.
(b) Renal Function[58] – Patients with severe renal impairment (creatinine clearance <50 ml/min and/or serum creatinine $\geq$3–4.0 mg/dl.) can be considered for autotransplantation, but only at a center with special expertise in this setting.
(c) Patient preference[59] – Since quality and length of outcome incorporate elements of personal choice, it is important to offer consideration of auto transplant in an open fashion.
(d) Cost utility[59,60] – In some health systems, costs preclude the use of auto transplantation.

Role of autotransplantation at the time of first relapse

Part of the decision process for autotransplant involves knowledge of the impact of waiting with a plan to transplant at relapse. French randomized trial data indicate **no** reduction in overall survival from waiting to do the transplant at relapse.[61] Quality of life becomes an important consideration. If transplant is not performed as a planned primary strategy, then typically additional therapy including maintenance is required with corresponding toxicity and side effects. Conversely, the major impact of the transplant is deferred, which for some patients can be a better personal choice.

Harvesting and storing stem cells for later use

There is a strong reluctance in many centers to harvest stem cells *without* a clear plan for use, typically immediate use. This reluctance arises from protocol priorities, cost/utilization constraints for harvesting and storage, as well as numerous other factors. Nonetheless, many patients request and want their stem cells harvested, even though they may not be enthusiastic about immediate HDT.

Recommendations

(a) Harvesting with storage for future use is a valid option. Depending upon local resources and facilities, stem cell storage may be reviewed on a case-by-case basis.
(b) There is a medical/scientific rationale for saving stem cells for later use.
(c) Delayed transplant is a viable treatment option. A repeat or second transplant in a patient is a viable option, especially if a first remission was of at least 1 year and especially $\geq$2 years duration. (See discussion below of 'double' transplantation.)

Role of double or tandem transplantation

- At present the role of double or tandem transplantation as a planned primary strategy is not definitely known.[62–65]
- The results with planned primary tandem transplant (total therapy I and II at the University of Arkansas) have been good. The median overall survival has been 68 months, with some groups having longer survival (eg, good risk: $>$9 years).
- Comparative studies, including the French randomized studies, have shown benefit in response rates and survival. The most recent follow-up analyses presented at ASH 2002[63] indicated statistically significant survival benefit with planned tandem transplant for patients with significant residual disease after the first transplant.

Recommendations

(a) At the present time, planned tandem transplant continues to be a clinical trial option and should be carried out at centers specialized in this approach.
(b) A second or repeat transplant in a patient who has responded well with a first transplant and relapsed after $\geq$2 years is a useful and viable option.[66]
(c) Saving and storing enough stem cells for a second or additional transplant, if appropriate, is strongly recommended.

Role of allogeneic transplantation

Details of results with allogeneic transplantation have been extensively reviewed.[67–70]

Despite medical improvements over the past two decades, allogeneic transplant, even with a perfectly

matched family member donor, is a high-risk procedure in the management of multiple myeloma. The initial treatment-related morbidity and mortality is high. Even at centers with the greatest experience, and in the best risk settings, initial mortality is at least 20%. In other centers, 20–30% or higher mortality is frequently reported. The pulmonary complications are usually the most critical for myeloma patients.

The potential advantages of allogeneic transplantation are the ability to collect myeloma-free stem cells and the graft versus myeloma effect. But, despite these factors, long-term cure is rare. Relapse continues at a rate of approximately 7% per year with long-term follow-up. Graft-versus-host disease can also be an ongoing problem, requiring therapy and impairing quality of life.

The graft-versus-myeloma effect can be enhanced by using donor lymphocyte infusions, which have been clinically beneficial in some series.[71]

There is recent interest in non-myeloablative or 'mini' allogeneic transplants in myeloma.[72] The intent is primarily to achieve a graft-versus-myeloma effect with lesser toxicity than with a matched full allogeneic transplant. However, although antimyeloma effects have been promising, with an 84% response rate in the first 32 patients in one series, the risks remain high with substantial acute (45%) and chronic (55%) graft-versus-host disease reported.

Overall recommendations

(a) Conventional full-match allogeneic transplantation is rarely recommended as a primary strategy because the risks of transplant-related complications are too high. However, allogeneic transplantation can be considered in younger patients, particularly in those with an HLA-matched, CMV-negative, sibling donor of the same gender, since the risks are lower.
(b) 'Mini' allogeneic transplantation[73] is a promising new approach, which requires further evaluation as part of well-planned clinical trials.
(c) Twin or syngeneic transplantation[74] is a rare option, which is a safe procedure with good outcome and is recommended when an identical twin is available.

Maintenance therapy

In this section, the role of ongoing anti-myeloma therapy will be considered.[75–79]

The role of anti-myeloma maintenance therapy following frontline therapy and/or stem cell transplantation is unclear.

It is generally agreed that therapy be continued following response (>50% reduction in M-component) until stable remission is achieved. At a minimum, this means two or three sequential measurements of M-component level at monthly intervals following maximum response. In the UK and Canadian MRC studies, the establishment of a stable plateau is an important end point and requires 4–6 months of stability.[80] Thereafter, the transition is to either no further therapy or maintenance of some sort. With the advent of stem cell transplantation, the decision is whether or not to give any therapy after recovery from engraftment post HDT.

Maintenance therapy is not definitively helpful in any disease setting.

Continued alkylator therapy is not beneficial in post M/P plateau.

Cycle active therapies are not useful since myeloma cell labeling indices are generally zero or very low in remission.[80]

Alpha interferon, after two decades of research, has proven to provide only marginal benefit overall.[78] Remission duration is prolonged by 4–7 months and there is no statistically significant impact on overall survival.

Low-dose prednisone (50 mg every other day) as maintenance showed benefit in a recent study evaluating both remission duration and survival. This SWOG study showed prolongation of remission from 5 to 14 months and median survival from 26 to 37 months.[79] Although this is very promising, prednisone maintenance can have significant side effects. Further studies of the benefits, side effects, and quality of life are required.

Several new agents are now being studied, including thalidomide, Revimid®, VELCADE™, as well as dendritic cell and other vaccine approaches.

Overall recommendations

(a) No strong recommendation can be made for any particular maintenance strategy.
(b) The pros and cons of specific maintenance therapy such as prednisone or alpha interferon must be assessed in the individual patient, based upon the level of residual disease and the anticipated potential for renewed disease activity. Steroids in some fashion are the simplest agents for maintenance if some therapy is deemed necessary. Also, alpha interferon can be considered, starting with a trial for tolerance, especially in settings in which benefit has been observed in some studies, including postautostem cell transplantation, IgA myeloma, and in the setting of concomitant viral infection such as hepatitis. Although no trial data exist, thalidomide with or without steroids is an option for maintenance, especially in high-risk settings. The potential for neuropathy can temper such use.

Supportive care and management of specific complications

TREATMENT OF BONE DISEASE:[81–89]

Approximately 80% of myeloma patients have lytic bone lesions and/or diffuse osteopenia secondary to myeloma.

Table 14 Bisphosphonate therapy

Recommended for
All myeloma-related bone disease[a]
Aredia®, Zometa®, and Clodronate® (or Bonefos®) are all beneficial in Myeloma[b]
Choice of bisphosphonate determined by
i.v. infusion time
Oral tolerance
Potential antimyeloma effects
Toxicities
Patient preference
Costs (individual/health authority)

[a]This includes patients with multiple plasmacytomata of bone and/or other situations in which active bone destruction is occurring. Therapy is not recommended for MGUS (Table 2):
Active myeloma patients *without* manifest bone disease are at risk of bone disease because of the potential for undetected bone disease and the osteopenic effects of ongoing steroid use. Such patients can be considered for ongoing bisphosphonate therapy; however, again the ASCO guidelines do not incorporate these patients.
[b]Other bisphosphonates such as Fosamax® and Actonel® are available but have not been specifically evaluated in myeloma.

Table 15 Bisphosphonate monitoring

Renal toxicity is a concern with all i.v. bisphosphonates, especially with chronic administration over many years (eg, ≥2 years).
Serum creatinine must be measured before each administration of i.v. bisphosphonate. An increase of ≥0.5 mg/dl may require dose/schedule adjustments[a]
Periodic urine protein measurement (24 h) is required (eg, q 3–6 months) with chronic administration, especially with Aredia at ≥2 years of use[b]
Longer infusion time is the best protection against potential toxicity, for example,
Aredia increase time of 90 mg infusion to 4 h
Zometa increase time of 4 mg infusion to 30–45 min
Dosage reduction, additional hydration, and less frequent administration are further options
Important risk factors for renal toxicity are
Age (>65 years)
Sex (female)
Prior renal dysfunction (especially serum. creatine ≥2 mg/dl)
Underlying disease, for example hypertension/diabetes
Concomitant drugs, for example, NSAIDs/thalidomide/other nephrotoxins (see Table 16) and/or prior AREDIA™
Bence Jones proteinuria

[a]Renal evaluation is required before proceeding with further doses.[93]
[b]Significant 'non Bence Jones' proteinuria (albuminuria) can occur, requiring renal evaluation.[94]

Treatment of the myeloma with chemotherapy and/or radiation therapy is very important for the control of bone disease.

Bisphosphonates, which substantially inhibit new bone destruction, are recommended as ongoing therapy for all myeloma patients with bone disease.

The details of recommendations for bisphosphonates are summarized in Table 14.

The bisphosphonates that are in general use are pamidronate (Aredia®), zoledronic acid (Zometa®), and clodronate (Bonefos®). Other oral agents such as Fosamax® and Actonel® have not been specifically studied in myeloma, although they are known to be helpful in preventing steroid-induced osteopenia. Overall these agents have proven to be equivalent in reducing what are called 'skeletal related events' or bone complications, such as fractures and pain.

Renal toxicity is a concern with bisphosphonates. Details are summarized in Table 15.

The incidence, types, and severity of renal complications are influenced by both the type of bisphosphonate and dose/speed/frequency of administration as well as patient factors, such as underlying renal disease, other nephrotoxic exposures, and type of myeloma, particularly light-chain disease or associated amyloidosis.

Careful monitoring is required along with proactive modifications in bisphosphonate administration as necessary. As listed in Table 15, serum creatinine measurement and 24-h urine collection are required as part of monitoring.

If serum creatinine measurement is not feasible before (eg, within 72 h before) each dose of i.v. bisphosphonate, one needs to carefully consider the options and risks. If risk factors for potential renal toxicity exist, Aredia® has a longer track record of safety and can be used preferentially in this setting. Albunimuria, although rare, is a more frequent risk with Aredia® over the long term (≥2years).

The ideal duration of bisphosphonate use is unknown. In general, it is recommended that bisphosphonates be continued indefinitely in all myeloma patients with bone disease. This is part of the ASCO guidelines.[85] *However*, formal quality of life and cost-effectiveness analyses have provided less definitive data, although generally favoring ongoing bisphosphonate use to reduce complications and analgesic needs.

Kyphoplasty provides a new tool that may impact bone care for myeloma patients. No large studies are available. However, in selected patients, the injection of liquid cement using the balloon technique may provide a safe approach for acute pain relief and improvement in structural integrity of collapsed vertebrae or other damaged bones.[90]

General measures to improve bone health are recommended including:

- Adequate pain control to allow ambulation and exercise.
- Radiation therapy and/or orthopedic surgery to restore structural integrity of bones and recovery of full mobilization. Radiation therapy should be used sparingly for acute problems such as:
  - spinal cord compression,
  - severe refractory pain and
  - to treat or prevent pathologic fracture.
- Since radiation therapy can impair local bone healing, many physicians prefer to use systemic steroids and/or other anti-myeloma therapy. Orthopedic surgery is used as necessary.
- Exercise, especially walking and/or swimming, is helpful to enhance bone strength and remodeling.

Carefully selected exercises to improve body strength, flexibility, and endurance can all be important.

- Avoidance of risky activities, which can increase the likelihood of falls and/or fractures, is recommended (eg, climbing ladders).
- Regular re-evaluation and follow-up testing of bones by X-ray/scan/ bone density testing to rule out new bone disease and assess the impact of treatment.

MANAGEMENT OF ANEMIA (91–97)

- Approximately 70% of myeloma patients have some degree of anemia at presentation. Median hemoglobin level is 10.5–11.0 g/dl.
- Persistent anemia (eg, hemoglobin <10.5–11 g/dl) is common especially in patients receiving ongoing therapy for myeloma.
- Reversible causes such as iron deficiency or Vitamin B_{12}/folate deficiency, hypothyroidism, or other causes should be sought and treated as necessary.
- Erythropoietin therapy should be considered for all patients with persistent symptomatic anemia. Details of different products and treatment schedules are summarized in Table 16.
- Transfusion of leukocyte-poor, washed, packed red blood cells is recommended when immediate improvement in circulatory oxygen-carrying capacity is required. Typically, this is only required if there is severe anemia at first presentation, following aggressive cytoreductive therapy such as stem cell transplantation, or in the setting of refractory disease.

MANAGEMENT OF RENAL PROBLEMS (98–103)

Renal function is a critical issue in myeloma management.

Multiple factors can affect renal function and are summarized in Table 17.

Prompt therapy is frequently required when renal function is impaired, either to directly treat the myeloma with chemotherapy and/or radiation or treat associated complications such as hypercalcemia, dehydration, hyperuricemia, hyperviscosity, ureteral obstruction, or infection.

Bence Jones (monoclonal light-chain excretion) myeloma and/or amyloidosis are particular risk factors for ongoing renal injury. Close monitoring is required. Hydration, alkaline diuresis, and plasmapheresis can all, at times, be critically important to recovery or improvement of renal function. Besides the level of monoclonal protein in the urine, the serum Freelite measurement can be very helpful to assess the magnitude of light-chain exposure to the kidneys.

Many medical conditions, drug treatments, and toxic exposures are especially dangerous for myeloma patients. Table 17 summarizes the most common problems. Specific preventive and/or treatment strategies may be necessary. In general, all potential nephrotoxins should be avoided. Special caution is required with nonsteroidal anti-inflammatory agents (NSAIDs), contrast dyes, and bisphosphonates.

Table 16 Use of erythropoietin

Indicated for
Anemia with hemoglobin <10 g/dl
Progressive or symptomatic anemia with hemoglobin 10–12 g/dl
Exclusions
Other causes of anemia, especially iron deficiency
Iron supplements should be used as necessary
Myeloma treatment
Since successful myeloma treatment usually improves anemia, erythropoietin therapy should be adjusted post-therapy
Loading dosage[a]
40 000 IU[2] is standard dose
Can continue as weekly dose
Can escalate to 60 000 U if no response after 4 weeks and/or no iron deficiency
Titrate to hemoglobin of 12 g/dl
Stop if hemoglobin >14 g/dl
Three times/week dosing
10 000 IU[2] three times/week is an alternate schedule
Can escalate to 20 000 IU if no response after 4 weeks and/or no iron deficiency
Titration and stopping as above

[a]This is for the unmodified recombinant products (eg, PROCRIT®; EPOGEN®). Standard q 2–3 week schedules are used for the longer acting darbopoietin alfa (NeoRecormon®, Aranesp®).

Table 17 Factors affecting renal function

Myeloma protein
Serum M-component especially IgD/A
Light chains
Glomerular light-chain deposition, especially kappa type
Tubular casts or amyloidosis, especially lambda type
Metabolic
Calcium elevation
Uric acid elevation
Volume depletion
Drugs/toxins
NSAIDs
Intravenous contrast (dyes)
Antimicrobial therapy, for example, aminoglycosides, Vancomycin, Ampho. B, Acyclovir
Other drugs, for example, high-dose chemotherapy (platinum/ cyclophosphamide), ACE inhibitors, diuretics, bisphosphonates (Aredia/Zometa), cyclosporine
Therapeutic radiation, for example, with stem cell transplant
Nonmyeloma renal factors
Glomerulonephritis
Diabetes mellitus
Hypertension
Renal cysts
Veno-occlusive disease
Graft-versus-host disease

THE LEVEL OF RENAL FUNCTION SIGNIFICANTLY AFFECTS SPECIFIC MYELOMA THERAPY.

Role of VAD and pulse dexamethasone (D) – Since melphalan is hydrolyzed and excreted, and Cytoxan metabolites are excreted via the kidneys, dose adjustments with renal impairment are required. Since dose calculations can be complex in the setting of active myeloma, VAD and dexamethasone alone are preferred since they can provide rapid efficacy, without concerns about renal clearance and/or toxicity.

HDT – As noted above, in the setting of renal impairment, HDT must be utilized with caution in specialized centers in the setting of renal impairment.

Patients with abnormal renal function not requiring dialysis – At least 20–30% of myeloma patients have or develop abnormal renal function during the course of the disease.

Elevated serum creatinine – Elevation in serum creatinine is the most common abnormality. Any degree of elevation is of concern and requires consideration as to etiology and treatment. Usually, any potential nephrotoxin, including NSAIDS and i.v. bisphosphonates,[102] should be withheld until the elevation is reversed and/or clarified. If the increase is due to increased myeloma activity, antimyeloma therapy may be required. Renal biopsy may be required to establish a diagnosis. The type and aggressiveness of therapy for renal insufficiency is influenced by the anticipated reversibility of the renal dysfunction. Reversibility is least likely when the serum creatinine is high (eg, $\geq$4 mg/dl) and/or if the dysfunction is of long duration. Nonoliguric renal failure is potentially more reversible if treated early.

Development of proteinuria – As a result of the disease and/or treatment, a nephrotic state can develop with, sometimes substantial, proteinuria (several g/day). Potential nephrotoxins, including i.v. bisphosphonates,[103] should be discontinued. Renal biopsy may be required to clarify the situation. Nephrotic states are more typically associated with glomerular abnormalities, including amyloid or light-chain deposition.

MANAGEMENT OF INFECTIONS.[104,105]

Infection is the single most dangerous complication for myeloma patients. Impaired clearing of infection is an integral part of the disease process, which affects both cell-mediated and humoral immunity. The infection risk is increased by cytotoxic therapy, which reduces neutrophils, and by glucocorticoids such as prednisone or dexamethasone, which reduce the immune response to opportunistic infections. Myeloma patients are therefore susceptible to the broad range of infectious agents including viruses, bacteria, mycobacteria, fungi, and other pathogens.

The most common infections at the time of presentation are:

- Streptococcus pneumoniae,
- Hemophilus influenzae, and
- Herpes zoster (shingles).

Infections are most likely at times of increased myeloma disease activity, including the first 3 months of frontline therapy and at relapse.

The first 3 months of frontline therapy are the highest risk period for infectious complications. It has been shown that prophylactic use of antibiotics during this time period can be helpful. Additional randomized studies are ongoing. Many investigators routinely use antibiotic therapy along with VAD or high-dose dexamethasone therapy, including prophylaxis for pneumocystis carinii using trimethoprin – sulfamethoxazole (eg, Bactrim).

With HDT and stem cell transplantation, antibiotic coverage and growth factor support are used routinely.

Aggressive treatment of serious infections – Serious infections typically occur in the setting of several risk factors, such as:

- active myeloma,
- neutropenia,
- steroid use,
- indwelling catheters/tubes/implants and
- underlying disease – for example, diabetes mellitus.

Owing to the diversity of potential infections, broad initial coverage is required along with growth factor support, as necessary. Intravenous gammaglobulin may be a helpful adjunctive measure for patients responding poorly with other measures. Extreme caution is required with regard to nephrotoxic agents. Every effort should be made to obtain cultures for specific identification of the pathogen(s) involved. Occult sites should be considered, including dental, sinuses, cerebrospinal fluid, cardiac vegetations, prosthetic implants and the like. Long-term antibiotic use may be required in these settings.

Management of hypercalcemia

- Hypercalcemia has become a less frequent complication of active myeloma because of earlier diagnosis and more routine use of bisphosphonate therapy.
- Typically, hydration and steroids (prednisone or dexamethasone) rapidly reverse hypercalcemia.
- Bisphosphonate therapy is used for persistent or severe hypercalcemia. A recent study showed zoledronic acid (Zometa®) 4mg to be more effective than pamidronate (Aredia®) 90mg.[106] Other measures such as calcitonin are rarely required.
- Truly refractory hypercalcemia is rare and usually occurs in the setting of refractory underlying myeloma. If renal failure ensues, dialysis is very effective management, if otherwise appropriate.

Novel therapies and new technologies

- Several novel therapies (Table 18) and new technologies (Table 19) are available.

Table 18 NOVEL THERAPIES

Phase II–III level
Thalidomide
Thalidomide analogs Revimid™/Actimid™
VELCADE™
Arsenic trioxide (Trisenox™)
Genasense BCl-2 antibody

Examples of agents in earlier development	*Description*
Farnesyl transferase inhibitors (FTIs)	FTIs induce apoptosis of myeloma cells in the lab and prevent their growth in response to IL-6. Clinical studies have been rather disappointing thus far
Histone deacetylase (HDAC) inhibitors	These agents, such as SAHA and LAQ842 (Novartis), induce apoptosis of myeloma cells in the lab; LAQ842 has also shown significant activity in a mouse model of myeloma. No clinical studies
Heat shock protein (Hsp) inhibitors	Hsp inhibitors promote cell survival and growth. 17-AAG, an Hsp inhibitor, prolongs survival in a mouse model of myeloma. Phase II trials in myeloma are planned
Insulin-like growth factor (IGF) receptor inhibitors	IGFs stimulate growth of myeloma cells and protect them from apoptosis. Inhibitors of the IGF receptor, such as ADW (Novartis), block these actions
(LPAAT)-b inhibitors	These agents induce apoptosis of myeloma cells. Several agents in this class developed by cell therapeutics are being investigated

Table 19 New technologies

Gene array technology
Serum Freelite™ test[9]
Whole-body FDG/PET scanning[15]
Snarecoil bone marrow biopsy needle

Table 20 Response rates: Phase II trial of revimid™ alone

Dose	*No. of Patients*	*Response (Bladé criteria[106])*		
		CR	*PR*	*MR*
15 mg 2 × daily	23	0	22%	43%
30 mg once daily	23	9%	13%	22%
Both doses	46	4%	17%	33%

Overall response, 54% (both doses; combining CR, PR, and MR).

Novel therapies[107–116]

The most promising novel therapies are:

- Thalidomide (Thalomid™) and thalidomide analogs Revimid™ and Actimid™.
- Bortezomib (VELCADE™).[107]
- Arsenic trioxide (Trisenox™).

Thalidomide:

Thalidomide continues to show benefit in a wide variety of settings.

Thalidomide plus dexamethasone is very active as a frontline approach (see frontline therapy: management of symptomatic multiple myclona).[44–48]

Thalidomide alone or combined with alpha interferon has shown early benefit as a maintenance strategy.[46] Further studies are required.

Low-dose thalidomide (50–100 mg/day) both alone and combined with dexamethasone improves survival in advanced multiple myeloma.[46,108] In the recent Italian study,[109] Thal/Dex as salvage therapy for advanced myeloma produced a 52% response rate (≥50% reduction in M-component) with a median progression-free survival of 12 months and median overall survival of 27 months, which is better than what is achievable with conventional chemotherapy salvage ($P < 0.05$).

Thalidomide is currently being evaluated as part of combination therapy in numerous studies (eg, plus melphalan or Cytoxan). Of particular interest, thalidomide plus bortezomib (VELCADE™) with or without dexamethasone has shown benefit in refractory myeloma post auto transplant with chromosome 13 deletion.[109]

REVIMID™ (CC-5013):

Preliminary results of a Phase II trial were presented at ASH 2002.[110] Table 20 summarizes the response rates at different dose levels of Revimid™.

Of note, dexamethasone enhanced response to Revimid™. Revimid™ appeared to have been well tolerated with no neurologic side effects such as neuropathy, sleepiness, or constipation in early testing. Neutropenia was a problem, which has led to a 3-week on/1-week off schedule for further testing. Several trials are now ongoing, including a Phase III trial of dexamethasone versus Revimid™ plus dexamethasone.

VELCADE™ (bortezomib, formerly PS-341):

Final results of the 202-patient, multicenter, Phase II 'SUMMIT' trial of VELCADE™ in heavily pretreated (six median prior lines of therapy) patients with relapsed and refractory myeloma were presented at

Table 21 RESPONSE TO VELCADE™ ALONE IN THE SUMMIT TRIAL

Response (Bladé criteria[106])	Percentage of patients
Complete response (IF neg)	4
Complete response (IF pos)[a]	6
Partial response	17
Minimal response	8
Stable disease	24
Overall response	35

[a]M-protein not measurable, but still detectable by immunofixation.

Table 22 RECENT TRISENOX™ TRIALS IN MYELOMA

Investigator	*Regimen*	*Objective response*[a]	*Stable disease*
Hussein	Trisenox™ + vitamin C	10/21 (48%)	8/21 (38%)
Lee	Trisenox™	2/6 (33%)	4/6 (67%)
Berenson	Trisenox™	2/7 (29%)	1/7 (14%)
Berenson	Trisenox™ + vitamin C + chemo	4/6 (67%)	1/6 (17%)

[a]Exact levels and durations of response not yet determined.

ASH 2002.[111] The response rates, according to the criteria defined by Blade[116] and confirmed by an independent review committee, are summarized in Table 21. The overall response rate (CR + PR + MR) was 35%. Of note, the median response duration was 12 months and median overall survival was 16 months This compares favorably to the 6–9 months survival in refractory patients reported in the literature. Results in earlier stage disease in the 'CREST' study were also presented.[112] These patients had received a median of one prior line of therapy, with a median of three prior regimens, including stem cell transplant in 48%. In the 'CREST' study, overall responses were 33% and 50% at doses of 1 and 1.3 mg/m^2. These studies were also evaluated using the response criteria of Bladé *et al*[116] In both Phase II studies, responses were independent of the number or type of prior therapies and were associated with improved quality of life.

Based upon these promising results, VELCADE™ has been approved by the FDA for the treatment of patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

VELCADE™ is currently the focus of a multicenter phase III ('APEX') randomized trial comparing VELCADE™ to high-dose dexamethasone in >600 patients at 80 sites in multiple myeloma patients who have relapsed following one to three prior lines of therapy.The primary end point is time to progression. 'APEX' will also assess the role of VELCADE™ as maintenance therapy in responders.

Ongoing studies indicate benefit in several combination studies including VELCADE™ plus thalidomide,[109] DOXIL™,[113] dexamethasone,[111] as well as more complex combinations.

Assessment of thalidomide, Revimid™ and VELCADE™ as new therapies

The potential future roles of these agents were actively discussed.

The costs and convenience of oral versus i.v. medications influence both patient preference and the ideal clinical settings for use. The strange nuances of authorization and reimbursement were noted.

Each of the three agents has already contributed to overall improvement in outcome and survival for patients with relapsing/refractory myeloma.

Thalidomide plus dexamethasone is already a valid option versus VAD as a frontline therapy. It appears that the efficacy may be equivalent, but careful trial comparisons are required. A total of 30–40% of newly diagnosed patients still need new options for frontline induction.

It is widely anticipated that the next steps include the assessment of all three new drugs in the frontline setting. Combinations with each other and with standard therapies will be assessed regarding improved efficacy. Preliminary results with thalidomide/dexamethasone/VELCADE™ and VELCADE™/DOXIL are very encouraging.

However, a range of different goals and end points require evaluation.

- *Primary induction.* Achieving response in patients unresponsive with current options is an important goal. Improving the response for all patients with maximum enhancement of stem cell harvesting capability is another end point.
- *Consolidation with HDT.* Enhancing the efficacy of high-dose melphalan or other options can prolong remission and survival.
- *Post induction/consolidation maintenance.* Extending remission and overall survival in this setting is very important.

It is likely that each new drug will have differential utility in these different situations. For example, the oral agents thalidomide/Revimid™ can be more readily considered as maintenance agents, especially Revimid™, which appears to lack neurotoxicity. The myelosuppression with Revimid™, especially when used post stem cell transplantation, may however complicate use in the maintenance setting. The i.v. drug VELCADE™ can be more easily integrated as part of induction and/or consolidation.

Arsenic trioxide (Trisenox®): results summarized in Table 21. Arsenic trioxide has been evaluated in several studies. It is currently too early to assess the overall response, response duration, and survival data.

Other agents that also show promise, but that are farther behind in development include:

- Farnesyl transferase inhibitor R115777.
- Genasense BCl-2 antibody.
- Beta-lapachone (a novel plant product).
- Antiestrogens.

- Anti-IL-6 monoclonal antibodies.
- Holmium 'skeletal targeted radiation'.[117]
- Histone deacetylase LAQ824.[114]
- Hsp 90 inhibitors.[115]

See also Table 18 and Catley *et al*,[114] Mitsiades *et al*,[115] Blade *et al*,[116] Giralt *et al*.[117]

Current clinical trials

See myeloma matrix and other details at the IMF website: www.myeloma.org.

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CORRIGENDUM

Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation

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The Hematology Journal (2004) **5(3),** in press. doi:10.1038/sj.thj.6200402

Correction to: The Hematology Journal (2003) **4**, 379–398. doi:10.1038/sj.thj.6200312

Since the publication of this article, the authors have identified several errors. These are corrected as follows:

Here is a corrected version of Table 8A.

Table 8A Serum β_2-microglobulin (β2 m) and serum albumin (S. Alb) staging

SWOG staging system[a]
Stage I
β_2M <2.5 mg/l
Stage II
β_2M ⩾2.5 <5.5 mg/l
Stage III
β_2M ⩾5.5 mg/l
S. Alb ⩾3.0 g/l
Stage IV
β_2M ⩾5.5 mg/l
S. Alb <3.0 g/l

[a]Jacobson J *et al.* A new staging system for multiple myeloma patients based on the Southwest. Oncology Group (SWOG) experience. *Br J Haematol* 2003; **122**: 441–450.

On p. 384, section heading *Initial chemotherapy for multiple myeloma*, the third bullet point should read:

- There are six major options. The pros and cons of each are summarized in Table 10. The following reflects discussions and assessments of published data.

On p. 385, section heading *Recommendations*, the third bullet point should read:

- Several variations on VAD are in use and are also acceptable alternatives (see Table 1).

On p. 386, section heading *Thalidomide plus dexamethasone*, the last sentence should read:

Currently, 200 mg of thalidomide a day is recommended, although lower doses such as 50–100 mg may be equally effective and less toxic (Tables 12 and 13).