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Considerations in the Management of Myeloma

More than 13,500 cases of multiple myeloma will have been diagnosed in the United States in 2000. Treatments are designed to prolong the symptom-free interval, overall survival, and quality of life. Despite the development of numerous treatment regimens, median survival remains less than 4 years. For a few patients, however, potentially curative therapy exists.

We will first review issues of diagnosis, estimation of prognosis, and measurement of response to therapy. The latter part of the article will address contemporary management options, with an emphasis on the ongoing clinical development of newer transplant approaches and drug applications.

When discussing prognosis and treatment options with patients, the physician should address the following basic issues: (1) What distinguishes the diagnosis of myeloma from other monoclonal gammopathies? (2) When in the disease course is treatment necessary? (3) Which drugs should be used for treatment? (4) How should noncytotoxic drugs, including interferon bisphosphonates, and growth factors be integrated? (5) Is high-dose therapy with stem-cell rescue or allogeneic bone marrow transplantation appropriate? Understanding these issues will be useful when planning a consolidated approach for all phases of the disease—from initial treatment and maintenance to salvage therapy and palliation. We are hopeful that these guidelines will provide a starting point from which risks and benefits can be individualized.

ABSTRACT

Multiple myeloma remains an incurable cancer. In recent years, progress in different drug classes has improved outcomes, but management has become more complicated. Areas such as prognostic classification, the increased use of high-dose chemotherapy with autologous stem-cell rescue, and a wider array of ancillary drugs must be integrated into recommendations for a consolidated treatment plan. Estimating prognosis is dependent on both clinical features and a growing list of laboratory tests. Autologous transplantation has been applied to an increasing proportion of patients, at different points in the disease process. Besides the age cut-off issue, there are still significant treatment choices to be made within the transplant technique. Newer drugs, most recently, thalidomide (Thalomid), may offer benefits independent of conventional cytotoxic drugs or steroids. Use of ancillary drugs, such as bisphosphonates, interferon, P-glycoprotein blockers, antibiotics, and growth factors, are also discussed. For the future, immunotherapy in the posttransplant setting appears promising. Ultimately, basic research must identify intracellular targets for the development of specific new-generation drugs.

Diagnosis

A referral for diagnosis of myeloma may result from abnormalities on routine tests or from a presentation with symptoms. Test abnormalities may occur at any stage of disease, but a presentation of symptoms is usually indicative of stage III disease. The physician must decide not only how to treat the patient, but also when.

Laboratory results, such as those showing anemia, hyperproteinemia, renal failure, or hypercalcemia, may explain the symptoms. Alternatively, infection, neurologic symptoms, abnormal bone imaging, or pathologic fracture, may lead more indirectly to the diagnosis. The need to improve symptoms may obviate the decision regarding *when* to proceed with treatment. However, more commonly, the decision will be based on the factors discussed below.

The initial parts of the diagnostic work-up algorithm from the 1998 National Comprehensive Cancer Network's (NCCN) Guidelines are in Table 1.[1] The major and minor diagnostic criteria of Durie and Salmon are reproduced in Table 2.[2] Examination of a unilateral marrow aspirate and biopsy

is the cornerstone of pathologic confirmation. Evaluation of a paraprotein is a frequent starting point, but light chain disease, immunoglobulin D, and nonsecretory myeloma diagnoses may be confirmed in the absence of a detectable paraproteins. Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia, and nonmalignant plasma-cell disorders may also have monoclonal paraproteins.[3,4] Smoldering or indolent myeloma, which may be managed initially with observation, should be considered before proceeding to treatment. Similarly, the following non-myeloma plasma-cell dyscrasias may bear consideration: monoclonal gammopathy of unknown significance (MGUS), plasmacytoma (bone or soft tissue), and Waldenström's macroglobulinemia.

While there is, in some cases, an apparent functional overlap of the therapeutic options (eg, alkylators, steroids for Waldenström's macroglobulinemia), distinct treatments are usually recommended. For example, a radiation dose of 40 cGy to 55 cGy would be recommended for plasmacytoma, compared to < 30 cGy for palliation of a symptomatic myeloma lesion.[1] The diagnosis should be clear before proceeding to treatment.

If the patient presents with MGUS or smoldering myeloma, a serial observation will be necessary to rule out progressive disease. Diagnostic criteria for MGUS, indolent myeloma, or smoldering myeloma (also described by Durie and Salmon) are in Table 3.[2] Solitary plasmacytomas are distinguishable by having noninvolved marrow findings away from the single site. Patients with solitary plasmacytoma of the bone will frequently convert to multiple myeloma and require long-term follow-up. Waldenström's macroglobulinemia—an infrequent and indolent disorder—is distinguished principally by the immunoglobulin M isotype paraprotein, a more lymphomatoid appearance of the malignant plasma cells, and a clinical course similar to low-grade NHL.

Prognostic Factors

The clinical staging system of Durie and Salmon, shown in Table 4,[2,3] is a usual starting point for treatment decisions and prognostic stratification. In the 25 years since its publication, additional factors to predict prognosis have been identified in multiple studies. These additional factors reflect tumor bulk, growth rate, biology, drug response, and organ-system reserve. The most frequently identified factor is the serum level of beta₂-microglobulin (B2-M).[5] New prognostic factors may often turn out to be closely correlated with previously identified factors, especially B2-M. A list of these prognostic factors, which are only partly evaluated for interdependence, is in Table 5. Clinical factors, such as stage and length of initial plateau phase,[6] remain as important as newer molecular factors.

Prognostic Stratification

Prognostic stratification serves two

purposes: (1) For the individual physician/patient relationship, the quantitation of the risk of rapid progression will give the patient a more precise estimate of prognosis and provide a useful basis for making treatment choices. (2) Another purpose is to achieve more balance in the stratification of randomized trials or in comparing treatments that are described in separate, nonrandomized studies. Analyses of prognostic factors that are continuous variables may be facilitated through the use of threshold values. However, while thresholds are useful for group comparisons, it may be intuitively unclear how to apply a threshold to an individual patient.

The relative prognostic importance of pretreatment factors (especially B2-M) can be compared to the importance of the assessment of treatment decisions. Studies[7-10] have consistently shown that biologic disease factors appear to be more important in predicting survival than the treatment decisions

Table 3

Non-Myeloma Diagnostic Criteria

- **Indolent Myeloma**
- 3 or fewer lytic bone lesions
- IgA paraprotein < 50 g/L
- IgG paraprotein < 70 g/L
- No symptoms
- No anemia < 10 g/L
- Normal calcium
- Normal creatinine

Smoldering Myeloma

- Indolent myeloma criteria and 10% to 30%
- Marrow plasma cells
- No bone lesions

MGUS

- IgG paraprotein < 35 g/L
- IgA paraprotein < 20 g/L
- Bence-Jones protein < 1 g/24 hrs
- < 10% marrow plasma cells
- No symptoms
- No bone lesions

IgA = immunoglobulin A; IgG = immunoglobulin G; MGUS = monoclonal gammopathy of unknown significance.

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being evaluated. Two polarized views may arise from implications of this hierarchy: (1) One view is that pair-matching or retrospective estimates do accurately gauge whether a new treatment causes an improvement of outcomes or whether the new treatment produces results that appear better merely as a reflection of the selection of a patient cohort with better prognostic features.[10-12] (2) The other view is that only prospective randomization provides a fair balance of known molecular prognostic features, performance status, disease stage, lead time, comorbidities, and available supportive care.[13] An unfortunate result of these views is that issues of selection bias and risk stratification may dominate comparative discussions of either retrospective or randomized trials. This is

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Table 4

Durie-Salmon Staging System

- A = BUN < 3 mg/dL; creatinine < 2 mg/dL
- B = BUN > 3 mg/dL; creatinine > 2 mg/dL

Stage I

- Low tumor mass (< $0.6 \times 10^{12}/m^2$)

All of

- Hgb > 10 g/dL
- IgG < 5 g/dL; IgA < 3 g/dL; Bence-Jones < 4 g/24 hours
- Ca: Normal
- 0 or 1 lytic bone lesion

Stage II

- Intermediate tumor mass (0.6 to $1.2 \times 10^{12}/m^2$) neither I nor III

Stage III

- High tumor mass (> $1.2 \times 10^{12}/m^2$)

Any of

- Hgb < 8.5
- IgG > 7 g/dL
- IgA > 5 g/dL
- Bence-Jones > 12 g/24 hours
- Ca >12 mg/dL (adjusted for albumin)
- Multiple lytic lesions

BUN = blood urea nitrogen; Ca = calcium; Hgb = hemoglobin; IgA = immunoglobulin A; IgG = immunoglobulin G.

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mentioned again below in relation to the phase II experience with autologous transplantation.

Measuring Response

The finding that the serum or urine paraprotein level is directly correlated with tumor burden allows for serial measurements and determination of progressive disease and treatment response. Progressive disease can be defined as a sustained > 25% rise of M protein, or the appearance of new bone lesions.[1] Table 6 provides a hierarchy of response categories.

The recommended frequency for quantitation of immunoglobulin is every other cycle of therapy, or every 3 to

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6 months in the observation or plateau phase of treatment.[1] The proposed target for quantitative myeloma tumor reduction has been honed because of dose intensification and new measurement techniques.

The question of whether improving the frequency of complete response or partial response will necessarily improve overall survival and event-free survival must be addressed empirically. For conventional therapy, a complete response does not show an advantage over a partial response for overall survival, although plateau duration does influence overall survival.[6]

A higher frequency of complete response and partial response occurs in autologous transplants than with conventional therapy. In the analysis of patients treated with up-front, tandem autologous transplant (see Arkansas Group's Total Therapy discussed later in this article), Barlogie et al found that achievement of a complete response, as opposed to a partial response, before the second transplant, resulted in an improved median survival (80+ vs 68 months, $P = .001$).[14]

With the advent of molecular techniques, the category of complete response (ie, histologically absent malignant marrow infiltrate and disappearance of paraprotein) has been refined. The molecular complete response is the subset of the clinical complete response, in which the malignant clone is not detected by sensitive polymerase chain reaction techniques. Based on the experience with other malignancies, a molecular complete response may be viewed as the rational prerequisite for potential cure.[15] Early analyses favor a better outcome (later relapses) for the subset of patients with a molecular complete response.[16]

Careful, empiric assessment of how these better complete responses imply or cause improvement of event-free survival and overall survival is necessary in the context of previous experience with conventional therapy. Conclusive proof of cure among patients achieving

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a molecular complete response (not just prolonged event-free survival) may develop in the coming years.

Treatment

Conventional Cytotoxics

Conventional chemotherapy can be divided into alkylator-based (usually oral) melphalan (Alkeran) and prednisone (MP), and non-alkylator-based (such as 96-hour continuous infusion) vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD). The high therapeutic index of steroids favors their inclusion in most regimens. Single-agent dexamethasone has activity without the side effects of cytotoxics.

Numerous published series over the last decades have compared different conventional therapy arms with a variety of alkylator, nitrosourea, steroid, vinca, and anthracycline combinations.[3,4] A 1992 meta-analysis showed that MP appears to be as good as other, more complex, toxic, and expensive regimens.[17] More recent analyses have reached a similar conclusion.[18,19]

Therapy with VAD offers the features of a more rapid response, without the use of alkylating agents, which may be toxic to stem cells. Even so, a series of 66 patients with stem cells collected at the point of salvage had only a 3% failure of stem-cell collection.[20] Like VAD, high-dose cyclophosphamide (Cytoxan, Neosar)—which also mobilizes stem cells—is frequently used in the pretransplant context. For salvage treatment, a non–cross-resistant regimen, such as etoposide, dexamethasone, ara-C, cisplatin (Platinol) (EDAP), VAD; or high-dose cyclophosphamide, may be used.[1,15]

Maintenance Therapy

Interferon After Conventional Therapy

The use of interferon alfa-2b (Intron A) for the maintenance of remission has been studied in detail in multiple randomized trials over the last 15 years. Some show no effect, some show a modest event-free survival benefit without an overall survival benefit, and a few demonstrate an overall survival benefit. The overall conclusion from this data remains controversial.

Synthesizing these independent, con-

Table 5

Prognostic Factors[2,3]

Disease Features

- Clinical stage (hemoglobin, paraprotein, calcium, renal function)[1,2]
- B2-M[1]
- CRP[1]
- PCLI[1]
- Lactate dehydrogenase[1]
- Presence of deletion 13 chromosome abnormality (for transplant)[47,71]
- Microvessel density[55,56]
- Peripheral blood monoclonal plasma cells > 4%
- P-gp expression
- Soluble IL-6 receptor
- Serum (shed) CD56
- Plasmablastic morphology

Response Features

- % of reduction: CR, PR, vs SD or worse
- Achievement of plateau
- Duration of plateau[6]
- Molecular CR vs clinical CR[16]

B2-M = beta-2-microglobulin; CR = complete response; CRP = C-reactive protein; IL-6 = interleukin-6; PCLI = plasma cell labeling index; P-gp = P-glycoprotein; PR = partial response; SD = stable disease.

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flicting reports, a balanced conclusion[21,22] suggests that the effect of interferon therapy after a complete or partial response from conventional chemotherapy is, at best, a several-month improvement of event-free survival (but not overall survival) for a minority (< 15%) of patients. A 1998 meta-analysis of 4,000 randomized patients, presented in abstract form, concluded that the benefit is 7 months of overall survival with $P < .03$.[23] Newly published studies with interferon randomization and various conventional treatments are similar to the earlier pattern—sometimes with a significant event-free survival advantage, but either a nonsignificant overall survival advantage[24] or no advantage.[25,26]

A decision to use interferon for postremission maintenance should be made

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Table 6

Hierarchy of Responses[a]

- Progressive disease (> 25% increase in M protein or new bony lesion)
- Stable disease/plateau phase
- Minimal response
- PR (PR, > 50% decrease in M protein)
- Very good PR (> 90% decrease in M protein)
- CR (CR, undetectable paraprotein, low marrow plasma cell %)
- CR (no clonal kappa/lambda population in marrow)
- CR (no PCR-detectable clonal rearrangement in marrow)
- Cure

ABMTR = Autologous Blood and Marrow Transplant Registry; CR = complete response; EBMT = European Blood and Marrow Transplant; IBMTR = International Bone Marrow Transplant Registries; PCR = polymerase chain reaction; PR = partial response.

[a]The Annotation of the EBMT, IBMTR, and ABMTR response definitions, authored by Bladé et al, provides a more detailed description, encompassing measurements other than just M protein.[72]

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recognizing that further study will be necessary to define which patient subsets may derive the most benefit.[22] Toxicity of interferon at the typical dose of 3 million units three times a week may include flu-like symptoms, depression, and fatigue. For most, the expense, toxicity, and inconvenience of the injections will accrue no survival benefit.

Steroids

Steroids have also been applied for the purpose of postconventional therapy maintenance. In the Southwest Oncology Group (SWOG) Study 9028, myeloma patients who had achieved at least a partial response after VAD chemotherapy were randomized between interferon or interferon/prednisone maintenance. The addition of prednisone to interferon resulted in a significant progression-free survival difference (19 vs 9 months, $P = .008$), but a nonsignificant overall survival advantage (57 vs 46 months, $P = .36$).[27]

Interferon After Transplant

An increased frequency of very low tumor burden is associated with molec-

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