TABLE 136-2 RISK STRATIFICATION IN MYELOMA

Chromosomal Abnormalities		
Method	**Standard Risk (80%) (expected survival 6–7+ years)**	**High Risk (20%) (expected survival 2–3 years)**
Karyotype	No chromosomal aberration	Any abnormality on conventional karyotype
FISH	t(11;14)	Del(17p)
	t(6:14)	t(4:14)
	Del(13)	t(14:16)
		t(14;20)

International Staging System		
	Stage	**Median Survival, Months**
β_2M <3.5, alb ≥3.5	I (28%)[a]	62
β_2M <3.5, alb <3.5 *or* β_2M = 3.5–5.5	II (39%)	44
β_2M >5.5	III (33%)	29
Other features suggesting high-risk disease:		
De novo plasma cell leukemia		
Extramedullary disease		
Elevated lactate dehydrogenate (LDH)		
High-risk gene expression profile		

[a]Percentage of patients presenting at each stage.

Abbreviations: β_2M, serum β_2-microglobulin in mg/L; alb, serum albumin in g/dL; FISH, fluorescent in situ hybridization.

Durie-Salmon staging system is unable to predict outcome and thus is no longer used. High labeling index, circulating plasma cells, performance status, and high levels of lactate dehydrogenase are also associated with poor prognosis.

Other factors that may influence prognosis are the presence of cytogenetic abnormalities and hypodiploidy by karyotype, fluorescent in situ hybridization (FISH)–identified chromosome 17p deletion, and translocations t(4;14), (14;16), and t(14;20). Chromosome 13q deletion, previously thought to predict poor outcome, is not a predictor following the use of newer agents. Microarray profiling and comparative genomic hybridization have formed the basis for RNA- and DNA-based prognostic staging systems, respectively. The ISS system, along with cytogenetic changes, is the most widely used method for assessing prognosis (Table 136-2).

TREATMENT MULTIPLE MYELOMA

No specific intervention is indicated for patients with MGUS. Follow-up once a year or less frequently is adequate except in higher risk MGUS, where serum protein electrophoresis, complete blood count, creatinine, and calcium should be repeated every 6 months. A patient with MGUS and severe polyneuropathy is considered for therapeutic intervention if a causal relationship can be assumed, especially in absence of any other potential causes for neuropathy. Therapy can include plasmapheresis and occasionally rituximab in patients with IgM MGUS or myeloma-like therapy in those with IgG or IgA disease. About 10% of patients with myeloma are asymptomatic (SMM) and will have an indolent course demonstrating only very slow progression of disease over many years. For these patients, no specific therapeutic intervention is indicated, although early intervention with lenalidomide and dexamethasone may prevent progression from high-risk SMM to active MM. At present, patients with SMM only require antitumor therapy when the disease becomes symptomatic with development of anemia, hypercalcemia, progressive lytic bone lesions, renal dysfunction, or recurrent infections. Patients with solitary bone plasmacytomas and extramedullary plasmacytomas may be expected to enjoy prolonged disease-free survival after local radiation therapy at a dose of around 40 Gy. There is a low incidence of occult marrow involvement in patients with solitary bone plasmacytoma. Such patients are usually identified because their serum M component falls slowly or disappears initially, only to return after a few months. These patients respond well to systemic therapy.

Patients with symptomatic and/or progressive myeloma require therapeutic intervention. In general, such therapy is of two sorts: (1) systemic therapy to control the progression of myeloma and (2) symptomatic supportive care to prevent serious morbidity from the complications of the disease. Therapy can significantly prolong survival and improve the quality of life for myeloma patients.

The therapy of myeloma includes an initial induction regimen followed by consolidation and/or maintenance therapy and, on subsequent progression, management of relapsed disease. The therapy is partly dictated by the patient's age and comorbidities, which may affect a patient's ability to undergo high-dose therapy and transplantation.

Thalidomide (200 mg daily), when combined with dexamethasone, achieved responses in two-thirds of newly diagnosed MM patients. Subsequently, lenalidomide (25 mg/d on days 1–21 every 4 weeks), an immunomodulatory derivative of thalidomide, and bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks), a proteasome inhibitor, have each been combined with dexamethasone (40 mg once every week) and obtained high response rates (>80%) in newly diagnosed patients with MM. Importantly, their superior toxicity profile with improved efficacy has made them the preferred agents for induction therapy. Efforts to improve the fraction of patients responding and the degree of response have involved adding agents to the treatment regimen. The combination of lenalidomide, bortezomib, and dexamethasone achieves close to a 100% response rate and 30% complete response rate, making it one of the preferred induction regimens in transplant-eligible patients. Other similar three-drug combinations (bortezomib, thalidomide, and dexamethasone or bortezomib, cyclophosphamide, and dexamethasone) also achieve >90% response rate. Herpes zoster prophylaxis is indicated if bortezomib is used, and neuropathy attendant to bortezomib can be decreased both by its subcutaneous administration and administration on a weekly schedule. Lenalidomide use requires prophylaxis for deep vein thrombosis (DVT) with either aspirin or warfarin or low-molecular-weight heparin if patients are at a greater risk of DVT. In patients receiving lenalidomide, stem cells should be collected within 6 months, because the continued use of lenalidomide may compromise the ability to collect adequate numbers of stem cells. Initial therapy is continued until maximal cytoreduction. In patients who are transplant candidates, alkylating agents such as melphalan should be avoided because they damage stem cells, leading to decreased ability to collect stem cells for autologous transplant.

In patients who are not transplant candidates due to physiologic age >70 years, significant cardiopulmonary problems, or other comorbid illnesses, the same two- or three-drug combinations described above are considered standard of care as induction therapy. Previously, therapy consisting of intermittent pulses of melphalan, an alkylating agent, with prednisone (MP; melphalan, 0.25 mg/kg per day, and prednisone, 1 mg/kg per day for 4 days) every 4–6 weeks was used. However, a number of studies have combined novel agents with MP and reported superior response and survival outcomes. In patients >65 years old, combining thalidomide with MP (MPT) obtains higher response rates and overall survival compared with MP alone. Similarly, significantly improved response (71 vs 35%) and overall survival (3-year survival 72 vs 59%) were observed with the combination of bortezomib and MP compared with MP alone. Lenalidomide added to MP followed by lenalidomide maintenance also prolonged progression-free survival compared with MP alone. These combinations of novel agents with MP also achieve high complete response rates (MPT, ~15%; MP plus bortezomib, ~30%; MP plus lenalidomide, ~20%; and MP, ~2–4%). Although combinations of MP with newer agents are an alternative