Multiple myeloma

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Summary

Multiple myeloma accounts for 10% of all hematologic cancers. Median age at diagnosis is 69 years for men and 72 years for women. The incidence of MM has remained relatively stable, but the associated mortality has declined since the early 1990s. The knowledge acquired about the bone marrow microenvironment in MM and the availability of new drugs has significantly improved patients survival in the past 10 years. Immunomodulatory drugs (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib, carfilzomib) can induce apoptosis of myeloma plasma cells and suppress cytokine release and metabolic ways which sustain the disease. These novel agents demonstrate substantial activity either alone or as part of a range of combination regimens. MM therapy is now based on 1 or 2 new drugs plus standard chemotherapy. Induction is patient tailored and first of all it depends on eligibility for stem-cell transplantation and key presenting features of the patients and the disease. Noteworthy, novel agent-based combination therapies may overcome most of poor prognostic factors. Up to 80% of newly diagnosed MM patients present with osteopenia, osteolysis and fractures. Thalidomide, lenalidomide and bortezomib have a beneficial effect on myeloma-related bone disease. Thalidomide reduces bone resorption, lenalidomide and bortezomib inhibit osteoclast growth and survival, and specifically target key factors in osteoclastogenesis, preventing development of osteolytic lesions. Noteworthy, new therapies offer higher complete response rates than previously reported with standard regimens.

KEY WORDS: multiple myeloma; immunomodulatory drugs; myeloma bone disease.

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by a proliferation of plasma cells in bone marrow (antibody-forming cells) and consequently an excess of monoclonal paraprotein. The accumulation of plasma cells interferes with the production of blood cells and can cause soft-tissue masses (plasmacytomas) and lytic skeletal lesions. Common presenting symptoms of MM are bone pain, pathologic fractures, anemia with consequent weakness and fatigue, hypercalcemia, spinal cord compression, renal failure, and pneumococcal or other infection. However, MM may also be asymptomatic and can be discovered through routine blood screening. MM is the second most common hematologic malignancy in the United States after non-Hodgkin lymphoma. It is estimated that there will be 20,520 new cases and 10,610 deaths from the disease in 2011 (1). MM is principally a disease of the elderly; the median age at diagnosis is 69 years for men and 72 years for women (2). Age at diagnosis affects the 5-year survival rate, which in 2001-2007 was 53% for patients diagnosed before age 65 years and 30% for those diagnosed at ≥ 65 years. The incidence of MM has remained relatively stable, but the associated mortality has declined since the early 1990s. According to the latest data available, the 5-year survival rate increased from 26% in 1975-1977 to 39% in 1999-2006. Between 1988 and 2006, the median survival for patients < 65 years of age increased from 3.7 years to 7.4 years and for those > 65 years of age from 3.3 to 3.7 years (3). Much of the improvement may be attributed to the advent of newer therapies, the immunomodulatory derivatives (IMiDS) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, as well as to the increased use of autologous stem cell transplantation (ASCT). The complex interaction between myeloma cells, stromal cells, T lymphocytes, osteoblasts and osteoclasts makes bone marrow microenvironment favorable to MM. Immunomodulatory drugs and proteasome inhibitors can induce apoptosis of myeloma plasma cells and suppress cytokine release and metabolic ways which sustain the disease. These novel agents demonstrate substantial activity either alone or as part of a range of combination regimens. Thus, MM therapy is now based on 1 or 2 new drugs plus standard chemotherapy. One of the notable aspects of these new regimens is that they offer higher complete response (CR) rates than previously reported with standard regimens. Achieving a CR has been shown to be prognostic for improved long-term outcomes, both in patients not eligible for high-dose therapy plus stem-cell transplantation (HDT–SCT) and in the transplant setting. CR has recently been recommended as an additional registration endpoint by the American Society of Hematology/US Food and Drug Administration (FDA) Workshop on Clinical Endpoints in Multiple Myeloma (4). However, the relationship between CR and prolonged overall survival (OS) is not always consistent and the qualitative impact of CR may vary among therapies. Thus, the CR rate is only one of several endpoints that must be considered; achieving a very good partial response (VGPR) is also important (5). Induction is patient tailored and first of all it depends on eligibility for stem-cell transplantation and the risk: benefit profiles of the various therapies assessed according to key presenting features of the patients such as age, comorbidities, impaired renal function, or a history of thrombosis. Patients with active MM should be further categorized by stage. This is most simply accomplished with the International Staging System, which relies simply on serum beta 2 microglobulin (B2M) and albumin levels (6). Stage I is B2M < 3.5 mg/L and albumin ≥ 3.5 g/dL. Stage II is neither stage I nor stage III. Stage III is B2M ≥ 5.5 mg/L. In validation studies, the median survi-

val of patients in stage I, 62 months, was more than twice that of patients in stage III, 29 months, and the median survival of patients in stage II was intermediate. An evolving understanding of risk associated with cytogenetic abnormalities has led the International Myeloma Working Group (IMWG) to evaluate the role of cytogenetic and FISH analysis in assigning risk. Poor risk abnormalities are a cytogenetically detected deletion of chromosomal 13, which is expressed as del(13), del(13q), or del(17p) or a translocation between chromosomes 4 and 14, which is expressed as t(4;14) or detection by FISH of t(4;14), t(14;16), or del(17p). Del(13) or del(13q) detected only by FISH in the absence of another abnormality does not imply substantially higher risk. High serum B2M level and International Staging System stage II and III do predict high risk. At present whereas some abnormalities denote higher risk and some of the newer therapies appear to overcome the higher risk, cytogenetic analysis should not be used to direct treatment (7).

Treatment options for elderly patients and those ineligible for HDT-SCT

Due to age or comorbidities at the time of diagnosis, more than half of MM patients may not be eligible for transplant; in these patients melphalan-prednisone (MP) was the standard of care for 40 years. MP results in response rates of up to 55% with a CR rate <5% and median OS of 2-3 years. Preclinical studies have demonstrated synergy between IMiDs and melphalan and between bortezomib and melphalan (8, 9). The addition of thalidomide to MP (MPT) resulted in significantly higher overall response rates (ORR) versus MP (57-76% vs. 31-48%), higher CR/VGPR and OS; MPT overcame the deleterious effect of adverse cytogenetics (chromosome 13 deletions) and advanced disease (10, 11).
In the VISTA trial (Velcade as Initial Standard Therapy in multiple myeloma), bortezomib (Velcade)-MP (VMP) demonstrated superiority versus MP across all efficacy endpoints, including ORR (71% vs. 35%, P < 0.001) and CR (30% vs. 4%, P < 0.001). VMP efficacy, in terms of response rate, time to progression (TTP) and OS were unaffected by the adverse prognostic impact of high-risk t(4;14), t(14;16), and del(17p) by FISH analysis (12). Updated results at a median follow-up of 3 years indicated that MPV reduced the risk for death by 35% compared with MP (13).
MPT and VMP have replaced MP as a standard of care and have been approved by the European Medicines Evaluation Agency (EMEA) for the front-line treatment of patients aged more than 65 years or who cannot be treated with HDT.
Phase 3 data on MP plus lenalidomide (Revlimid) have not been yet published, however, MPR is showing promise in older patients. In a phase 1/2 trial that involved newly diagnosed patients ≥ 65 years of age, MPR resulted in a CR rate of 24% and an overall response rate of 81%; results comparable to those of HDT. Myelosuppression with MPR was greater than with MPT/MPV but manageable and peripheral neuropathy did not occur. MPR overcame the adverse prognostic effects of del(13) or t(4;14) (14).

Treatment options for patients eligible for transplant

HDT-SCT is a standard of care in patients aged up to approximately 65-70 years (15, 16). Due to higher efficacy novel-agent-based induction regimens have replaced vincristine plus doxorubicin and dexamethasone (VAD), the standard induction prior transplant. Preclinical studies showed that both thalidomide and lenalidomide potentiate the activity of dexamethasone (D) and that additive activity is indicated between bortezomib and highdose dexamethasone (8), providing the rationale for clinical investigation of these combination regimens. TD induction prior to HDT-SCT demonstrated superior ORR (63% vs. 41%, P = 0.0017) and prolonged time to progression (TTP), median 22.6 months vs. 6.5 months, versus dexamethasone (15). A significantly higher post-induction ORR was achieved with bortezomib–dexamethasone versus VAD (P < 0.0001), which translated into a significantly higher VGPR rate post-transplant (57% vs. 38%, P = 0.0003) (16).
The GIMEMA Italian Myeloma Network trial demonstrated a marked increase in the CR/near CR rate post-induction with VTD versus TD (32% vs. 12%, P < 0.001). VTD was highly active in patients with poor prognostic cytogenetics or high tumour burden. The high-quality response translated into a significantly improvement in post-transplant quality of response (17).
It is imperative that induction therapy does not compromise stem-cell viability or collection in transplant-eligible patients. Bortezomib, alone or in combination, does not adversely affect stem-cell harvesting or engraftment as shown following VD and VTD (18).

Maintenance or consolidation therapy

Thalidomide maintenance therapy following HDT provided a significant event free survival (EFS) benefit in patients without a chromosome 13 deletion (P < 0.006), and in patients achieving <VGPR (P < 0.004) (19). Single ASCT followed by six months of thalidomide maintenance also appeared to be an effective strategy and superior to double ASCT (20). Molecular remissions have been associated with VTD consolidation therapy post-ASCT (17).
Recently, two phase III intergroup study of lenalidomide versus placebo maintenance therapy following single ASCT reported a 50% advantage in PFS with lenalidomide maintenance (21, 22).
A phase 3 study comparing MPR *vs* MP and then lenalidomide maintenance *vs* placebo found that patients receiving MPR had significantly improved response rates. In the maintenance portion of the study, lenalidomide maintenance was associated with a 69% reduced risk for progression compared with placebo (23).
All these data suggest the patient would be best served by continuing maintenance therapy.

The IMiDs and bortezomib in the setting of MM bone disease

Bone disease is key presenting feature of MM and a key diagnostic criteria for MM (24, 25). Up to 80% of newly diagnosed MM patients present with osteopenia, osteolysis and fractures. Myeloma-induced bone destruction occurs as a result of increased osteoclast activity, which is not accompanied by a comparable increase in osteoblast function (26). The IMiDs and bortezomib both have a beneficial effect on myeloma-related bone disease. Thalidomide reduces bone resorption but does not affect osteoclast function and bone formation. Lenalidomide and bortezomib inhibit osteoclast growth and survival, and specifically target key factors in osteoclastogenesis, preventing development of osteolytic lesions (27, 28).

The IMiDs and bortezomib in the setting of renal impairment

Renal impairment is present in approximately 30% of patients at diagnosis (24). Pharmacokinetic studies show that no dose reduction of thalidomide is required (28). Bortezomib can be administered at the full approved dose and schedule; dosing adjustments are not necessary even for those patients requiring dialysis (29). Novel agent combinations therapies, including VTD, induce rapid response leading to recovery of renal function in most of the patients; removing the need for dialysis in some patients. Although lenalidomide (usually at a modified dose) may be used in patients with renal disease, bortezomib-based regimens are more

generally recommended because bortezomib is principally metabolized by the liver and its clearance is independent of renal function (30-32).

Conclusion

Thalidomide, bortezomib and lenalidomide have changed the standard of care for the management of MM. Response rates and quality of responses previously only seen with HDT-SCT are now achievable with new induction regimens. Furthermore, these novel agents combine well with traditional therapies, and in some cases with one another, and are generally well tolerated in the front-line setting, including in patients with poor prognostic characteristics. Clinical studies are addressing the question whether or not there is an advantage for early SCT in patients already achieving a high quality of response.

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