Published in final edited form as:

Cancer J. 2009 ; 15(6): 473. doi:10.1097/PPO.0b013e3181c60f08.

Novel Therapies in Multiple Myeloma for Newly Diagnosed Non-Transplant Candidates

Sigurdur Yngvi Kristinsson, MD, PhD¹, Ola Landgren, MD, PhD², and Vincent S Rajkumar, MD³

¹Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden

²Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

³Division of Hematology, Mayo Clinic, Rochester, MN USA

Abstract

In the 21st Century, melphalan-prednisone can no longer be regarded as the standard treatment of multiple myeloma patients not eligible for high-dose melphalan followed by autologous stem cell transplantation. The introduction of thalidomide, lenalidomide and bortezomib has improved the arsenal of therapeutic options in multiple myeloma. Indeed, randomized studies have shown that melphalan-prednisone-thalidomide and melphalan-prednisone-bortezomib are superior to melphalan-prednisone alone. Additionally, other combinations, including lenalidomide are under study. In this review we discuss the role of novel therapies in multiple myeloma in elderly multiple myeloma patients. Important aspects, such as toxicity and the role of prognostic factors, are also addressed.

Introduction

Multiple myeloma is a malignant B-cell disorder characterized by a monoclonal proliferation of plasma cells in the bone marrow.(1,2) In a recent prospective cancer screening study including 77,469 healthy subjects, among who 71 developed multiple myeloma during the course of the study, multiple myeloma was consistently preceded by the precursor condition monoclonal gammopathy of undetermined significance (MGUS). (3) Multiple myeloma accounts for about 10% of hematological malignancies.(4,5) The median age at diagnosis is about 65-70 years and is only occasionally diagnosed in patients below 40 years of age.(4-6) Males are affected more commonly than females (7); compared to Caucasians, Blacks have higher rates of both MGUS and multiple myeloma (8). MGUS and multiple myeloma are 2- to 3-fold more common among blood relatives of MGUS/multiple myeloma patients (9-11). In the Western world, the annual age-adjusted incidence for multiple myeloma is 4.8-8 per 100,000.(5)

In multiple myeloma, the proliferation of B-cells commonly results in overproduction of monoclonal immunoglobulins, termed M-proteins. Approximately 8% of all patients are asymptomatic at diagnosis.(12) Clinical signs and symptoms may be caused by direct tumor growth or the monoclonal products. The malignant proliferation of plasma cells produces skeletal destruction that leads to bone pain and pathologic fractures. The M-protein may lead

to renal failure, hyperviscosity syndrome, or through suppression of uninvolved immunoglobulins result in recurrent infections. Anemia and hypercalcemia are common complications.(13)

Prognostic factors

A number of prognostic factors have been identified in various multiple myeloma patient populations and following different therapies. Today, the International Staging System (ISS) is the most widely used prognostic scoring system, and provides a simple and reproducible three-stage classification: stage I is characterized by β_2 -microglobulin less than 3.5 mg/L and serum albumin higher than 3.5 g per 100 mL and had a median survival of 62 months; stage II is represented by neither stage I nor III and showed a median survival of 44 months; and stage III is defined by β_2 -microglobulin above 5.5 mg/L with a median survival of 29 months (Table 1).(14)

Patients with symptomatic multiple myeloma may be classified into high-risk or standard-risk disease (Table 2).(15,16) Acquired chromosomal abnormalities significantly impact survival in myeloma patients. In current clinical practice, poor prognosis is associated with the presence of immunoglobulin heavy chain translocations t(4;14), t(14;16), t(14;20), deletion 17p13 or deletion 13. By contrast, a favorable prognosis has been observed in the presence of t(11;14), t(6;14) or hyperdiploidy. (17-20) In research settings, gene expression profiling (GEP) has become an increasingly powerful tool with the aim to characterize prognostic profiles (21), and define distinct multiple myeloma subtypes.(22,23)

It must be noted that the ISS and the adverse impact of cytogenetic abnormalities, as well as by GEP, are established in the context of conventional therapies but not with novel treatments. Also other factors, such as age at diagnosis, performance status, and response to therapy are of importance in the prognosis of multiple myeloma patients.(24,25)

Indications for therapy

At this time, there are no data to support that asymptomatic multiple myeloma patients benefit from early treatment.(26) Therefore therapy shall not be given to asymptomatic multiple myeloma patients in clinical practice. However, clinical trials are currently ongoing in order to determine if new agents can delay progression from asymptomatic to symptomatic myeloma, and thereby prolong survival.

Patients with a diagnosis of multiple myeloma and with symptomatic disease are in need of therapy. Based on our overall aim to improve and develop new therapeutic strategies and novel drugs, we are in strong support of clinical trials in multiple myeloma. For patients that are not eligible for clinical trials, or if clinical trials are not available, in a standard clinical setting, one may separate multiple myeloma patients into those who are eligible versus those who are ineligible for high-dose melphalan therapy followed by an autologous stem cell transplant (16). In most institutions, patients considered ineligible for autologous stem cell transplantation are those greater than 65-70 years of age, with a serum creatinine >2.5 mg/dL, ECOG performance status 3 or 4, or New York Heart Association functional status class III or IV, or a combination. Patients with renal failure may be transplanted, but the morbidity and mortality is higher.(27). Given the high median age at diagnosis and concurrent morbidity, the majority of all multiple myeloma patients are not eligible for autologous stem cell transplantation.

The development of novel treatments in multiple myeloma

Since the 1960s, oral melphalan and prednisone (MP) has been the standard of therapy for patients not eligible for autologous stem cell transplantation.(28,29) Until recently, MP was considered standard of care for symptomatic patients older than 65-70 years. Based on several

clinical trials, the response rate with MP is only 50-60% and complete remissions (CR) are rare. This is reflected in a median overall survival of 24 to 48 months.(28,29) Consequently, through the years, many clinical trials have been conducted to develop treatment regimens with higher response rates and improved overall survival compared to MP. In a large meta-analysis of 4,930 symptomatic myeloma patients in 20 prospective trials, the response rate was 60% for combination chemotherapy compared to 53% for MP ($p < 0.001$). However, there was no difference in survival. Also the meta-analysis failed to identify a subset of patients who benefited from additional combinations of chemotherapy (28).

The discovery of novel therapies, including thalidomide, bortezomib and lenalidomide, targeting both myeloma cells and the bone marrow microenvironment, has changed the paradigm of myeloma therapy, especially for the elderly population. Thalidomide and lenalidomide have been found to have anti-angiogenesis properties, stimulate T- and natural killer cells and interfere with cytokines. They suppress growth factors such as interleukin-6, tumor necrosis factor- α , inhibit myeloma cell adhesion and blood vessel growth cytokines such as vascular endothelial growth factor.(30,31)

Bortezomib, a proteasome inhibitor, specifically interferes with the 26S proteasome, which is responsible for degrading protein that control transcription, the cell-proliferation cycle and metabolism.(32) Interestingly, although the initial rationale for its use in multiple myeloma was inhibition of NF-kappa-B activity by blocking proteasomal degradation of I-kappa-B-alpha, recent work indicates that bortezomib-induced cytotoxicity cannot be fully attributed to inhibition of canonical NF-kappaB activity in multiple myeloma. (33)

Combinations of novel agents with steroids, alkylating agents or anthracyclines have significantly improved response rates, progression-free survival (PFS), and overall survival in multiple myeloma.(34-40) There is also evidence that novel agents may overcome the poor prognosis induced by chromosomal abnormalities and ISS score. Below we review and discuss results and toxicities from major studies based on novel multiple myeloma drugs.

Thalidomide-based Regimens

Thalidomide combined with melphalan-prednisone

Recently, MP has been combined with thalidomide (MPT) in five different randomized studies (Table 3). Palumbo et al. reported a randomized trial (GIMEMA trial) comparing MPT with MP in 255 patients with newly-diagnosed myeloma aged 65 to 85 years who were considered ineligible for an autologous stem cell transplant.(41) The patients were randomized to six 4 week cycles of melphalan (4 mg/m^2 on days 1-7) and prednisone (40 mg/m^2 on days 1-7) or MP plus thalidomide 100 mg daily (MPT) during the six cycles and then as maintenance until sign of relapse or progressive disease. The response rate was 76% and CR 16% in the MPT regimen, compared to 48% and 2%, respectively, for MP. The two-year event-free survival was 54% vs. 27%, while the three-year survival was 80% vs. 64%, favoring the MPT regimen, although not significantly (41). In a recent update of that trial, after a median follow-up of 38 months there was still a significantly superior PFS in the MPT arm. However the median overall survival was similar, 45 months in the MPT group and 47.6 in the MP group.(42)

Grade 3-4 adverse events occurred in 48% with the MPT regimen, compared to 25% for MP. The risk of thromboembolic phenomena (12% vs. 2%) was significantly increased in the MPT group. Because of that the protocol was amended and enoxaparin 40 mg per day was given, during the first four cycles as anticoagulation prophylaxis, with a reduction in the number of events. Additionally infections (10% vs. 2%), peripheral neuropathy (8% vs. 0%), and constipation (6% vs. 0%) were greater in MPT compared to MP.

In the second study, the IFM 99-06, the French Myeloma Group reported on 447 previously-untreated patients with myeloma aged 65 to 70 years who were ineligible for autologous stem cell transplantation.(43) They were randomized to 12 cycles of 6-weeks melphalan (0.25 mg/kg) and prednisone (2mg/kg) (days 1-4) and thalidomide (given in an increasing dosage to a maximum of 400 mg daily if tolerated during the cycles and then stopped); or melphalan and prednisone in the same dosage and schedule; or VAD followed by melphalan 100 mg/m² × 2 followed by stem cell rescue. A higher partial response (PR) rate was seen in the MPT and in the melphalan 100 mg/m² groups, compared with MP (76 vs. 65 vs. 35%, respectively). Similarly, the CR rates were significantly higher with MPT (13%) and intermediate-dose melphalan (18%) compared with MP (2%). Median PFS was 27.5 months in the MPT patients and 17.8 months in the MP group ($P<0.0001$), and median overall survival was significantly better in the MPT group compared to the MP group (51.6 and 33.2 months, respectively ($P<0.001$) and the melphalan 100 mg/m² group ($P=0.027$).(43)

Compared to the MP group, MPT was associated with higher rates of grade 3 or 4 neutropenia (48%), constipation (10%), and somnolence, fatigue/dizziness (8%). Patients did not receive anticoagulation, and 12% of the patients in the MPT arm developed venous thromboembolism.

In another French study (IFM 01-01), 229 patients with previously untreated multiple myeloma who were greater than 75 years of age, were randomized to melphalan 0.2 mg/kg plus prednisone 2 mg/kg days 1-4 every 6 weeks for 12 cycles or melphalan and prednisone in the same dosage plus thalidomide 100 mg daily (MPT) without maintenance.(44) The PR rate was 62% in the MPT group and 31% in the MP group, and CR was observed in 7% and 1% respectively. Median PFS was 24.1 months for MPT and 19.0 months for MP ($P=0.001$), and median overall survival was 45.3 months for MPT and 27.7 months for MP ($P=0.03$).(44)

Toxicity in this elderly population was similar to that observed in earlier trials. Peripheral neuropathy was seen in 39% in the MPT group compared to 21% in the MP group. Grade 3-4 neutropenia was greater in the MPT arm. No anticoagulation was prospectively planned, and no significant difference was observed in thrombosis complication between the arms, possibly related to more frequent use of anti-thrombotic treatments for other co-morbidity in this age group.(44)

In a study by the Nordic Myeloma Study Group, 362 patients with a mean age of 75 years (range, 49–92) were randomized to receive melphalan (0.25 mg/kg) and prednisone (100 mg) for four days every 6 weeks until plateau phase.(45) The MPT arm received additionally thalidomide at a starting dose of 200 mg, escalating to 400 mg if possible, and then given as maintenance as 200 mg in plateau phase. Results of an interim analysis showed better PR (27% vs. 22%) and CR/nCR (6% v. 3%) in the MPT group compared to MP. No difference was observed in PFS or overall survival (29 vs. 33 months) in this study. Furthermore in patients above 75 years there was a tendency to higher early mortality in the MPT group.

No thrombosis prophylaxis was given and there was no difference in the incidence of thromboembolic complications, however approximately 30% of the patients had anti-thrombotic treatment for other reasons.(45)

In the HOVON study, 344 patients age 65 years and older were randomized to receive eight 4-week cycles of melphalan (0.25 mg/kg days 1-5), prednisone (1 mg/kg days 1-5) with or without 200 mg of thalidomide, until plateau.(46) The MPT arm additionally received thalidomide as maintenance, 50 mg per day. The overall response rates were higher in MPT group (66% vs. 47%) and CR was 2% in both arms. The PFS was significantly improved in the MPT group ($P<0.001$). Median overall survival was 37 months in the MPT group compared to 30 months in MP (not significant).

Grade 2-4 toxicity was seen in 60% of the patients in the MP arm and in 88% of the MPT patients, and was mainly due to peripheral neuropathy. No differences between the two arms were seen for other toxicities.(46)

Taken together, results from these five randomized studies have been consistent with regards to response rate being superior in the MPT arms compared to MP, however all but one have shown an improvement in PFS. Only the two French studies have shown a survival benefit. Comparisons between different studies are difficult to make because of differences in patient populations, duration of treatment and use of maintenance regimens. Despite these differences, data strongly support the MPT regimen as the new standard of care for elderly myeloma patients. In all studies, the MPT patients showed a higher incidence of extra-hematological toxicities compared with the MP regimen, especially neurological adverse events, infections, and thromboembolism. Anti-thrombotic prophylaxis is recommended when using MPT, and aspirin seems to be a safe option.(24) The higher toxicity rate significantly reduced the efficacy of the MPT combination. Randomized studies that used more strict inclusion criteria showed better outcome. In the French studies, a higher incidence of grades 3–4 hematological toxicity (neutropenia and thrombocytopenia) was also observed, probably due to a higher number of MP cycles administered (12 cycles) and a higher dose of thalidomide (median dose 200 mg). The duration of MP treatment may also be reduced from 12 cycles to 6 cycles, as prolonged melphalan exposure induces thrombocytopenia that hampers the delivery of subsequent effective salvage regimens.

Other thalidomide combinations

In younger patients, Thal/Dex significantly improves PFS in comparison with high-dose dexamethasone alone.(34) In 289 elderly patients, Thal/Dex was compared with MP in a randomized study. Patients in the Thal/Dex arm had a significantly higher response rate but failed to show any advantage in PFS. In fact, overall survival was inferior with Thal/Dex compared with MP ($P=0.024$). (47) Patients on Thal/Dex experienced more grades 2–3 neuropathy (25%) and skin toxicity (12%) compared with those on MP (8 vs. 3%, respectively), particularly in patients older than 75 years with poor performance status. Thromboembolic complications were seen in 8% of patients receiving Thal/Dex and in 3% of patients receiving MP. The higher toxicity rate of Thal/Dex regimen can explain the lower efficacy of Thal/Dex in the elderly population.

In the Medical Research Council Myeloma IX trial, cyclophosphamide, thalidomide and dexamethasone (CTD) was compared with MP in 900 patients. In the CTD group, the PR rate (82 vs. 49%) and the CR rates (23 vs 6%) were significantly superior in the CTD group. (48) Data on remission durations are not available, and mature survival data are needed on this trial prior to making recommendations for clinical practice.

Bortezomib based-regimens

Bortezomib combined with melphalan-prednisone

The Spanish cooperative group conducted a large phase I/II trial of melphalan, prednisone, and bortezomib, (MPV), with encouraging results.(49) This study formed the basis for the VISTA trial, where 682 patients, median age 71 years (range 48-91), were randomized to receive 9 six-week cycles of bortezomib 1.3 mg/m² intravenously days 1, 4, 8, 11, 22, 25, 29, 32 during cycles 1-4 and bortezomib 1.3 mg/m² on days 1, 8, 22, and 29 during cycles 5-9 plus melphalan 9 mg/m² and prednisone 60 mg/m² days 1-4 of each cycle (MPV) or to MP in the same dosage and schedule.(50) The response rates were better in the MPV arm, both PR (71% vs. 4%) and, importantly a very high CR was observed in the MPV arm (30% vs. 4%). Median survival was not reached in either group but at 16 months the survival was significantly improved in the

MPV arm ($P=0.008$). Furthermore, the efficacy seemed not to be influenced by poor prognostic factors, including ISS stage, renal failure, and high risk cytogenetic profiles.(50)

As expected, neutropenia, thrombocytopenia, anemia, and gastrointestinal symptoms were more common with the MPV regimen. Peripheral neuropathy occurred in 44% of the MPV group and in 5% with MP; This included 13% risk of grade 3 neuropathy in the MPV arm. The peripheral neuropathy resolved or improved in 74% of patients within a median of two months. (50) Pre-existing neuropathy or previous neurotoxic therapy increases the risk of peripheral neuropathy, which can be reduced or resolved by prompt dose reduction of the drug. The incidence of neuropathy can also be reduced greatly by once weekly administration of bortezomib instead of the twice-weekly schedule. There is an increased risk of herpes zoster infection with MPV, and prophylactic antiviral medications are recommended. There was no difference in the incidence of venous thromboembolism between the groups.

Lenalidomide-based regimens

Lenalidomide combined with melphalan-prednisone

The Italian group evaluated in a phase I/II trial, dosing, safety and efficacy of melphalan plus prednisone and lenalidomide (MPR) in newly diagnosed elderly myeloma patients.(51) The maximum tolerated dose was considered to be melphalan at 0.18 mg/kg on days 1–4, prednisone at a 2-mg/kg dose on days 1–4 and lenalidomide at 10 mg on days 1–21, every 28 days for nine cycles. Aspirin was given as a prophylaxis for thrombosis. Eighty-five percent of patients achieved at least a PR, and 23.8% achieved immunofixation-negative CR. The 1-year event-free and overall survival was 92 and 100%, respectively. Preliminary results showed that the event-free survival of patients with deletion of chromosome 13 or chromosomal translocation (4;14) was not significantly different from those who did not have such abnormalities.(51) The results of an international phase III study comparing MP vs MPR are awaited. An Eastern Cooperative Oncology Group (ECOG) study comparing MPT versus MPR is ongoing.

Grades 3–4 adverse events in the Italian study were mainly related to hematologic toxicities (neutropenia 66%). Severe non-hematologic side effects were less frequent and included febrile neutropenia (8%), cutaneous rash (10%) and thromboembolism. Neutropenia and DVT are the major complications with lenalidomide, although the addition of aspirin markedly reduced the risk of thromboembolic events in newly diagnosed patients treated with lenalidomide in association with dexamethasone or chemotherapy.(51) Recommendations for thromboprophylaxis in patients treated with thalidomide or lenalidomide have been published, and aspirin seems to be the preferred choice in the absence of additional risks of thromboembolism. (24) The addition of granulocyte-colony stimulating factor is recommended in case of neutropenia, and melphalan dose reduction (from 0.18 to 0.13 mg/kg) should be applied in the presence of severe neutropenia despite granulocyte-colony stimulating factor.

Lenalidomide with high-dose vs. low-dose dexamethasone

A randomized trial from the ECOG group studied 445 previously untreated symptomatic multiple myeloma. Patients were assigned to lenalidomide (25 mg daily days 1 to 21) plus high-dose dexamethasone (40 mg daily on days 1 to 4, 9 to 12, and 17 to 20) or to lenalidomide in the same dose and schedule plus dexamethasone 40 mg given weekly for each 28-day cycle. (52) The median age was 66 years, and included 233 patients older than 65 years. Among all patients preliminary results show that the one-year survival was 96% for lenalidomide/low-dose dexamethasone compared to 88% for lenalidomide plus high-dose dexamethasone. Early deaths were more common in the high-dose arm. The two-year survival probability was 87%

and 75%, respectively.(52). Among elderly patients the 2-year survival was also superior in the low-dose group.

There was significantly more grade 3-4 toxicity among patients in the low dose dexamethasone group (34% vs. 52%), including infections, fatigue, venous thrombosis. The risk of deep venous thrombosis was less in the low dexamethasone regimen (6% vs. 25%), as was the incidence of infections (7% vs. 14%).(52) Based on these results, a randomized trial comparing lenalidomide plus low dose dexamethasone and MPT has been initiated, and accrual is ongoing.

Maintenance therapy

There are a few studies on thalidomide maintenance after autologous stem cell transplantation, suggesting that it may improve outcome in a subset of patients with high risk myeloma or a poor response after autologous stem cell transplantation.(36,53-56) However, there are no studies supporting maintenance therapy after MPT or MPV. Currently, patients are treated for a fixed duration of 18 months with MPT with no maintenance based on the French studies. (43,44) Similarly, with MPV, the treatment duration is for 12 months followed by no maintenance. Lenalidomide is better suited to maintenance, but little data are available. At Mayo Clinic, if patients are treated with lenalidomide plus low-dose dexamethasone, patients are offered the option of continuing lenalidomide until progression after 12-18 months of treatment.

Summary and future directions

Similar to historical drugs, the efficacy of novel multiple myeloma regimens have to be balanced against their higher toxicities. At present in elderly patients, MPT, MPV, MPR, and lenalidomide plus low-dose dexamethasone have all shown significant clinical activity. Treatment with MPT and MPV are supported by phase III trials showing superiority in overall survival compared with MP. Lenalidomide and low dose dexamethasone had the advantage of low toxicity. Randomized trials have not compared these regimens, and in the absence of such trials, the choice of regimen should take into account several factors. Although the numbers are small, it appears that MPV overcomes the adverse effect of chromosomal abnormalities (50). Thus in the presence of high risk cytogenetic features (Table 2), as well as in patients at high risk for thromboembolism, and in patients with renal insufficiency, MPV is the preferred option, whereas MPT is preferred for patients with standard risk disease. Lenalidomide plus low dose dexamethasone is a reasonable alternative to MPT. MPR is also an emerging alternative. There is no evidence that continued chemotherapy with melphalan and prednisone is of benefit after achieving a plateau state, and hence treatment with MPT and MPV is given for a fixed duration of time. There is a risk of myelodysplasia from continued treatment with alkylating agents.

Management of complications in patients with multiple myeloma is also important, especially in the elderly with more co-morbidity. Recommendations on the management of complications such as skeletal disease, hypercalcemia, anemia, renal insufficiency, infections and thrombosis have been published.(13,24,57)

Results from three population-based studies (one registry-based Swedish study, one registry-based U.S. SEER study, and one hospital-based study from the Mayo Clinic, MN), indicate that survival in multiple myeloma has improved in recent years, after the introduction of the novel agents.(58-60) However, in all the improvement was predominantly observed in the younger patients. A limitation of these investigations is the fact that none of the three studies had detailed information on individual patients' clinical characteristics or therapy. Underlying causes of the absence of improvement in long-term survival among elderly patients remain unclear and are probably multifactorial, including increased co-morbidity among older

patients. Early mortality has been reported to be higher among elderly patients.(61) In addition to the fact that patients do not tolerate aggressive treatment such as high dose therapy, it has also been proposed that elderly patients present with a more advanced disease at diagnosis. (62,63) Results from randomized studies indicate that survival has improved in elderly patients with multiple myeloma with the introduction of novel agents. Innovative agents and procedures suitable for the older patient (>70 years) coupled with better prognostic markers used to guide individualized treatment in multiple myeloma are greatly needed.

In the shorter perspective, a key clinical challenge will be to better define the optimal sequence, combination(s), and use of available novel multiple myeloma drugs. In the future, molecular diagnostics/prognostics together with more targeted designed drugs and integrated molecular monitoring, will likely become increasingly important to explain clinical heterogeneity, to provide more personalized treatment strategies, and thereby improve survival for multiple myeloma patients. (21)

Acknowledgments

Supported in part by Grants CA62242 and CA107476 from the National Cancer Institute, Bethesda, MD.

References

1. Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance. *Br J Haematol* Sep; 2006 134(6):573–89. [PubMed: 16938117]
2. Swerdlov, SH.; Campo, E.; Harris, NL.; Jaffe, ES.; Pileri, SA.; Stein, H., et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlov, SH.; Campo, E.; Harris, NL.; Jaffe, ES.; Pileri, SA.; Stein, H., et al., editors. IARC; Lyon: 2008.
3. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* May 28;2009 113(22):5412–7. [PubMed: 19179464]
4. Ries, LAG.; Eisner, MP.; Kosary, CL., editors. SEER Cancer Statistics Review, 1975-2001. National Cancer Institute; Bethesda, MD: 2004.
5. Socialstyrelsen. Cancer Incidence in Sweden 2006. Stockholm; Sweden: 2007.
6. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* Jan;2003 78(1):21–33. [PubMed: 12528874]
7. Landgren O, Kyle RA. Multiple myeloma, chronic lymphocytic leukaemia and associated precursor diseases. *Br J Haematol* Dec;2007 139(5):717–23. [PubMed: 18021086]
8. Landgren O, Weiss BM. Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. *Leukemia*. Jul 9;2009
9. Kristinsson SY, Bjorkholm M, Goldin LR, Blimark C, Mellqvist UH, Wahlin A, et al. Patterns of hematologic malignancies and solid tumors among 37,838 first-degree relatives of 13,896 patients with multiple myeloma in Sweden. *Int J Cancer*. Apr 22;2009
10. Landgren O, Kristinsson SY, Goldin LR, Caporaso NE, Blimark C, Mellqvist UH, et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. *Blood* Jul 23;2009 114(4): 791–5. [PubMed: 19182202]
11. Vachon CM, Kyle RA, Therneau TM, Foreman BJ, Larson DR, Colby CL, et al. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood* Jul 23;2009 114(4):785–90. [PubMed: 19179466]
12. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* Jun 21;2007 356(25): 2582–90. [PubMed: 17582068]

13. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* Oct 28;2004 351(18):1860–73. [PubMed: 15509819]
14. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. *J Clin Oncol* May 20;2005 23(15):3412–20. [PubMed: 15809451]
15. Dispenzieri A, Rajkumar SV, Gertz MA, Fonseca R, Lacy MQ, Bergsagel PL, et al. Treatment of newly diagnosed multiple myeloma based on mayo stratification of myeloma and risk-adapted therapy (mSMART): consensus statement. *Mayo Clin Proc* Mar;2007 82(3):323–41. [PubMed: 17352369]
16. Stewart AK, Bergsagel PL, Greipp PR, Dispenzieri A, Gertz MA, Hayman SR, et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. *Leukemia* Mar;2007 21(3):529–34. [PubMed: 17230230]
17. Smadja NV, Bastard C, Brigaudeau C, Leroux D, Fruchart C. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood* Oct 1;2001 98(7):2229–38. [PubMed: 11568011]
18. Fonseca R, Blood E, Rue M, Harrington D, Oken MM, Kyle RA, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood* Jun 1;2003 101(11):4569–75. [PubMed: 12576322]
19. Gertz MA, Lacy MQ, Dispenzieri A, Greipp PR, Litzow MR, Henderson KJ, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood* Oct 15;2005 106(8):2837–40. [PubMed: 15976175]
20. Avet-Loiseau H, Attal M, Moreau P, Charbonnel C, Garban F, Hulin C, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. *Blood* Apr 15;2007 109(8):3489–95. [PubMed: 17209057]
21. Anguiano A, Tuchman SA, Acharya C, Salter K, Gasparetto C, Zhan F, et al. Gene Expression Profiles of Tumor Biology Provide a Novel Approach to Prognosis and May Guide the Selection of Therapeutic Targets in Multiple Myeloma. *J Clin Oncol*. Jul 27;2009
22. Zhan F, Tian E, Bumm K, Smith R, Barlogie B, Shaughnessy J Jr. Gene expression profiling of human plasma cell differentiation and classification of multiple myeloma based on similarities to distinct stages of late-stage B-cell development. *Blood* Feb 1;2003 101(3):1128–40. [PubMed: 12393520]
23. Carrasco DR, Tonon G, Huang Y, Zhang Y, Sinha R, Feng B, et al. High-resolution genomic profiles define distinct clinico-pathogenetic subgroups of multiple myeloma patients. *Cancer Cell* Apr;2006 9(4):313–25. [PubMed: 16616336]
24. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* Feb; 2008 22(2):414–23. [PubMed: 18094721]
25. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* Jul 11;1996 335(2):91–7. [PubMed: 8649495]
26. Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rodger S, Westin J. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I--a randomized study. Myeloma Group of Western Sweden. *Eur J Haematol* Feb;1993 50(2):95–102. [PubMed: 8440364]
27. Badros A, Barlogie B, Siegel E, Roberts J, Langmaid C, Zangari M, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *Br J Haematol* Sep;2001 114(4):822–9. [PubMed: 11564069]
28. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. *J Clin Oncol* Dec;1998 16(12):3832–42. [PubMed: 9850028]
29. Alexanian R, Haut A, Khan AU, Lane M, McKelvey EM, Migliore PJ, et al. Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *Jama* Jun 2;1969 208(9):1680–5. [PubMed: 5818682]
30. Corral LG, Haslett PA, Muller GW, Chen R, Wong LM, Ocampo CJ, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol* Jul 1;1999 163(1):380–6. [PubMed: 10384139]

31. Dredge K, Marriott JB, Macdonald CD, Man HW, Chen R, Muller GW, et al. Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *Br J Cancer* Nov 4;2002 87(10):1166–72. [PubMed: 12402158]
32. Mitra-Kaushik S, Harding JC, Hess JL, Ratner L. Effects of the proteasome inhibitor PS-341 on tumor growth in HTLV-1 Tax transgenic mice and Tax tumor transplants. *Blood* Aug 1;2004 104(3):802–9. [PubMed: 15090453]
33. Hideshima T, Ikeda H, Chauhan D, Okawa Y, Raje N, Podar K, et al. Bortezomib induces canonical NF- κ B activation in multiple myeloma cells. *Blood*. May 12;2009
34. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* Jan 20;2006 24(3):431–6. [PubMed: 16365178]
35. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood* Jul 1;2005 106(1):35–9. [PubMed: 15761019]
36. Barlogie B, Pineda-Roman M, van Rhee F, Haessler J, Anaissie E, Hollmig K, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood* Oct 15;2008 112(8):3115–21. [PubMed: 18492953]
37. Jagannath S, Durie BG, Wolf J, Camacho E, Irwin D, Lutzky J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. *Br J Haematol* Jun;2005 129(6):776–83. [PubMed: 15953004]
38. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* Jun 16;2005 352(24):2487–98. [PubMed: 15958804]
39. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* Nov 22;2007 357(21):2123–32. [PubMed: 18032762]
40. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* Nov 22;2007 357(21):2133–42. [PubMed: 18032763]
41. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* Mar 11;2006 367(9513):825–31. [PubMed: 16530576]
42. Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood* Oct 15;2008 112(8):3107–14. [PubMed: 18505783]
43. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* Oct 6;2007 370(9594):1209–18. [PubMed: 17920916]
44. Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Efficacy of Melphalan and Prednisone Plus Thalidomide in Patients Older Than 75 Years With Newly Diagnosed Multiple Myeloma: IFM 01/01 Trial. *J Clin Oncol*. May 18;2009
45. Waage A, Gimsing P, Juliusson G, Turesson I, Fayers P. Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: a placebo controlled randomized phase 3 trial. *Blood* 2007;110 Abstract 78a.
46. Wijermans P, Schaafsma M, van Norden Y, Ammerlaan R, Wittebol S, Sinnige H, et al. Melphalan + Prednisone Versus Melphalan + Prednisone + Thalidomide in Induction Therapy for Multiple Myeloma in Elderly Patients: Final Analysis of the Dutch Cooperative Group HOVON 49 Study. *Blood* 2008;112 Abstract 649.

47. Ludwig H, Hajek R, Tothova E, Drach J, Adam Z, Labar B, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood* Apr 9;2009 113(15):3435–42. [PubMed: 18955563]
48. Morgan G, Davies FE, Owen RG, Rawstrom AC, Bell S, Cocks K, et al. Thalidomide combinations improve response rates; results from the MRC IX study. *Blood* 2007;110 (Abstract 3593).
49. Mateos MV, Hernandez JM, Hernandez MT, Gutierrez NC, Palomera L, Fuertes M, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. *Blood* Oct 1;2006 108(7):2165–72. [PubMed: 16772605]
50. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* Aug 28;2008 359(9):906–17. [PubMed: 18753647]
51. Palumbo A, Falco P, Corradini P, Falcone A, Di Raimondo F, Giuliani N, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA--Italian Multiple Myeloma Network. *J Clin Oncol* Oct 1;2007 25(28):4459–65. [PubMed: 17785703]
52. Rajkumar SV, Jacobus S, Callander N, Fonseca R, Vesole D, Williams MV, et al. Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (ERA03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome wi. *Journal of Clinical Oncology* 2008;26 Abstract 8504.
53. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* Mar 9;2006 354(10):1021–30. [PubMed: 16525139]
54. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* Nov 15;2006 108(10):3289–94. [PubMed: 16873668]
55. Abdelkefi A, Ladeb S, Torjman L, Othman TB, Lakhal A, Romdhane NB, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. *Blood* Feb 15;2008 111(4):1805–10. [PubMed: 17875806]
56. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol* Apr 10;2009 27(11):1788–93. [PubMed: 19273705]
57. Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* Jun 10;2007 25(17):2464–72. [PubMed: 17515569]
58. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol* May 20;2007 25(15):1993–9. [PubMed: 17420512]
59. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* Mar 1;2008 111(5):2521–6. [PubMed: 17901246]
60. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* Mar 1;2008 111(5):2516–20. [PubMed: 17975015]
61. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol* Dec 20;2005 23(36):9219–26. [PubMed: 16275935]
62. Anagnostopoulos A, Gika D, Symeonidis A, Zervas K, Pouli A, Repoussis P, et al. Multiple myeloma in elderly patients: prognostic factors and outcome. *Eur J Haematol* Nov;2005 75(5):370–5. [PubMed: 16191085]
63. Lenhoff S, Hjorth M, Westin J, Brinch L, Backstrom B, Carlson K, et al. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. *Br J Haematol* May;2006 133(4):389–96. [PubMed: 16643445]

Table 1

Stage	Criteria
I	Serum β 2-microglobulin [lt]2.5 mg/L and Serum albumin [mt] 35 g/L
II	Not stage I or III
III	Serum β 2-microglobulin [mt] 5.5 mg/L

Table 2

High-risk Cytogenetic Features

By Fluorescent in-situ hybridization

- Translocation t(4;14)
- Translocation t(14;16)
- Deletion 17p-

By Conventional Karyotyping

- Hypodiploidy
 - Deletion chromosome 13
-

Table 3
Recent Randomized Trials in Non-Transplant Candidates with Newly Diagnosed Myeloma

	GIMEMA	IFM 99-06	IFM 01-01	NMSG	HOVON	VISTA
Number of patients	331	447	232	363	344	682
Median age (range)	72 (60-85)	69 (65-75)	78.5 (75-89)	75 (49-92)	72	71 (48-91)
MP regimen	6 4-week cycles	12 6-week cycles	12 6-week cycles	6-week cycles until plateau	8 4-week cycles	9 6-week cycles
Melphalan dose	4 mg/m ² days 1-7	0.25 mg/kg days 1-4	0.2 mg/kg days 1-4	0.25 mg/kg days 1-4	0.25 mg/kg days 1-5	9 mg/m ² days 1-4
Prednisone dose	40 mg/m ² days 1-7	2 mg/kg days 1-4	2 mg/kg days 1-4	100 mg days 1-4	1 mg/kg days 1-5	60 mg/m ² days 1-4
Thalidomide dose	100 mg	Up to 400 mg	100 mg	Up to 400 mg	200	Bortezomib*
Maintenance	Yes	No	No	Yes	Yes	No
PR	60.4 vs. 45.2	76 vs. 35	62 vs. 31	27 vs. 22	36 vs. 37	33 vs. 31
CR	15.5 vs. 2.4	13 vs. 2	21 vs. 7	15 vs. 6	2 vs. 2	30 vs. 4
PFS (months, median)	21.8 vs. 15.5	27.5 vs. 17.8	24.1 vs. 18.5	16 vs. 14	13 vs. 10	24 vs. 16***
OS (months, median)	45.0 vs. 47.6	51.6 vs. 33.2	44.0 vs. 29.1	29 vs. 33	37 vs. 30	No reached***

* Bortezomib 1.3 mg/m² days 1, 4, 8, 11, 22, 25, 29, 32 in cycles 1-4 and on days 1, 8, 22, and 29 during cycles 5-9

** Time to progression

*** Hazard ratio 0.61 (P=0.008) in favour of MPV