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Treatment of newly diagnosed myeloma

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Abstract

The introduction of thalidomide, bortezomib and lenalidomide has dramatically changed the treatment paradigm of multiple myeloma (MM). In patients eligible for autologous stem cell transplant (ASCT), combinations including thalidomide/dexamethasone (Thal/Dex) or bortezomib/dexamethasone (Bort/Dex) or lenalidomide/dexamethasone (Rev/Dex) have been introduced as induction regimens in patients eligible for ASCT. New induction regimens have significantly increased complete response rate before and after ASCT with a positive impact on progression-free survival. Maintenance therapy with thalidomide, under investigation with lenalidomide, may further prolong remission duration. In patients not eligible for ASCT, randomized studies have shown that melphalan, prednisone, thalidomide (MPT) and melphalan, prednisone and bortezomib (MPV) are both superior to melphalan and prednisone (MP), and are now considered standard of care. Ongoing trials will soon assess if MP plus lenalidomide may be considered an attractive option. More complex regimens combining thalidomide or bortezomib or lenalidomide with cyclophosphamide or doxorubicin have been also tested. In small cohorts of patients bortezomib or lenalidomide may overcome the poor prognosis induced by deletion 13 or translocation t(4;14) or deletion 17p13. If these data will be confirmed, a cytogenetically riskadapted strategy might become the most appropriate strategy.

Keywords

new drugs; therapy; diagnosis; myeloma

Introduction

Multiple myeloma (MM) accounts for approximately 10% of hematological malignancies, the frequency is constantly increasing due to aging of the general population.[1,2] At present, about 35% of myeloma patients are younger than 65 years, 28% are 65–74 years and 37% are older than 75 years.[3] The current changes of the demographic curves will probably increase the incidence of elderly patients in the near future. In some patients, symptomatic myeloma evolves from an asymptomatic benign stage termed MGUS. In others, an intermediate asymptomatic premalignant stage referred to as smoldering MM can be

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Conflict of interest

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recognized. The overall risk of progression from smoldering to symptomatic myeloma is 10% per year for the first 5 years, approximately 3% per year for the next 5 years and 1% for the next 10 years. The significant risk factors for progression included the amount of monoclonal protein and the extend of bone marrow involvement.[4] No differences in overall survival were noted in patients with *de novo* myeloma or in those with a preceding diagnosis of plasma cell disorder such as MGUS or smoldering myeloma.[5] To avoid the risk of an undue therapy in asymptomatic myeloma, the start of treatment requires the presence of at least one organ damage defined by hypercalcemia, anemia, renal insufficiency or bone lesions (CRAB criteria), which clearly define the occurrence of symptomatic myeloma.

Recently, agents with novel mechanisms of action, such as thalidomide, bortezomib and lenalidomide, have shown significant activity in MM. Thalidomide and lenalidomide have antiangiogenesis 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.[6,7] Bortezomib, a first in class proteasome inhibitor, specifically interferes with the 26S proteasome, which is responsible for degrading protein that control transcription, the cell-proliferation cycle and metabolism.[8] Combinations of these agents with steroids, alkylating agents or anthracyclines have significantly improved response rate and progression-free survival (PFS). In a large group of newly diagnosed myeloma patients, no difference in overall survival was reported during a 24-year period from 1971 to 1994, there was a trend toward improvement during the period 1995–2000 and a statistically significant benefit in overall survival was shown during the last 6 years (2001–2006).[9] These data suggest that autologous stem cell transplant (ASCT) was responsible for the trends seen during 1994–2000, while novel agents contributed to the improvement observed since 2001.

In newly diagnosed myeloma patients younger than 65 years, induction regimens including dexamethasone plus thalidomide or bortezomib or lenalidomide followed by high-dose melphalan and ASCT have significantly increased response rate. In elderly patients, usually older than 65 years, oral melphalan and prednisone (MP) has been combined with thalidomide or bortezomib significantly improving response rate and PFS.

The future challenge is to define the optimal sequence and combination of these drugs to significantly impact the natural history of the disease. This paper will focus on the role of new drugs for frontline treatment of MM.

Diagnosis

A monoclonal protein can be detected by serum protein electrophoresis alone in 82% of patients and by serum immunofixation in 93%; a combination of serum and urine protein immunofixation studies improve the sensitivity to 97%.[10] Less than 3% of patients have no evidence of monoclonal paraproteins (non-secretory myeloma). The serum immunoglobulin-free light-chain assay negates the need of immunofixation and 24-h urine electrophoresis for purposes of diagnosis; the assay also allows the quantitative monitoring of patients with oligo-secretory or non-secretory myeloma. In addition, the baseline-free light-chain measurement represents a prognostic factor for myeloma.[11] The diagnosis of MM requires 10% or more monoclonal plasma cells in the bone marrow and/ or a presence of biopsy proven plasmacytoma, monoclonal protein in the serum and/or urine (except in patient with true non-secretory myeloma) and presence of end-organ damage felt related to the underlying plasma cell proliferative disorder: hypercalcemia (serum calcium >10 mg/l), renal insufficiency (serum creatinine >2mg per 100 ml), anemia (hemoglobin <10 g per 100 ml), bone lytic lesions detected by skeletal survey.[12]

Prognostic factors

The clinical course of MM is quite heterogeneous: some patients die from disease evolution within few weeks, whereas others live for more than 10 years. Although very useful, it must be noted that most of the following parameters were studied before the advent of new active agents, and hence we need additional studies in the present era of novel therapy.

The International Staging System (ISS) provides a simple, powerful and reproducible three-stage classification: stage I is characterized by β_2-microglobulin less than 3.5 mg/l plus serum albumin ≥3.5 g per 100 ml and showed a median survival of 62 months; stage II is represented by neither stage I nor III and exhibited a median survival of 44 months; and stage III is defined by β_2-microglobulin ≥5.5 mg/l with a median survival of 29 months.[13] Acquired chromosomal abnormalities have shown to significantly impact survival in myeloma patients. Poor prognosis has been 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.[14–16] In a large study, the prognostic value of deletion 13 was almost entirely dependent on the association with t(4;14) and deletion 17p13. On a multivariate analysis, patients lacking t(4;14) and deletion 17p13 with a low β_2- microglobulin value had an excellent prognosis with a 4-year overall survival at 83%; patients presenting a single alteration either t(4;14) or deletion 17p13 or high β_2-microglobulin value had an intermediate prognosis; while patients showing the cumulative alterations t(4;14) plus deletion 17p13 plus high β_2- microglobulin had a very poor prognosis with a median survival of only 19 months.[16] It must be noted that the adverse impact of these cytogenetic abnormalities is firmly established in the context of conventional therapies but not with novel treatments. Bortezomib was shown to overcome the poor prognosis induced by deletion 13 and t(4;14) and deletion 17p13, whereas there is currently only preliminary data on efficacy with lenalidomide. [17,18] It is now strongly recommended that all newly diagnosed myeloma patients be tested at minimum for t(4;14), t(14;16) and deletion 17p13 by fluorescence *in situ* hydridization together with measurements of serum β_2-microglobulin and lactate dehydrogenase.[19]

Treatment

There is little evidence that early treatment of patients with asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage. Clinical trials are ongoing to determine if new agents can delay progression of smoldering myeloma. Treatment choices are mainly based on age and presence of comorbidities. Preliminary data show that new drugs may overcome the poor prognosis induced by chromosomal aberrations such as deletion 13, t(4;14) or deletion 17p13.

Treatment of myeloma in patients eligible for transplantation

Initial therapy for patients is dependent on eligibility for ASCT, mainly determined by age, performance status and coexisting comorbidities. Protracted melphalan-based therapy should be avoided in patients with newly diagnosed myeloma who are considered eligible for ASCT, as it can interfere with adequate stem cell mobilization. Typically, patients are treated with approximately 2–4 cycles of induction therapy before stem cell harvest. This includes patients who are transplant candidates but who wish to reserve ASCT as a delayed option for relapsed refractory disease. Such patients can resume induction therapy following stem cell collection until a plateau phase is reached, reserving ASCT for relapse.

The present choices for initial therapy are thalidomide/ dexamethasone (Thal/Dex), bortezomib/dexamethasone (Bort/ Dex) and related bortezomib-based combination

regimens, and lenalidomide/dexamethasone (Rev/Dex). These regimens act rapidly and are associated with high-response rates; Thal/Dex and Rev/Dex have the added advantage of being orally administered. Thal/Dex and Rev/Dex are associated with an increased risk of deep vein thrombosis (DVT), necessitating routine thromboprophylaxis. New combinations including thalidomide, bortezomib or lenalidomide with chemotherapy agents, such as doxorubicin or cyclophosphamide, are currently under investigation.

Thalidomide-based regimens

Thalidomide and dexamethasone combination has increasingly been used instead of VAD. In 2005, a case-matched control analysis showed that response rates with Thal/Dex were superior to those achieved with VAD (76 vs 52%).[20] Randomized trials confirmed these findings.[21–23] The Eastern Cooperative Oncology Group (ECOG) compared Thal/Dex to high-dose dexamethasone alone in 470 newly diagnosed myeloma patients. The overall response rate was significantly higher with Thal/Dex compared with dexamethasone (63 vs 46%; $P<0.001$). Time to progression was significantly longer with Thal/Dex compared with dexamethasone (median, 22.6 vs 6.5 months, $P<0.001$). DVT was more frequent with Thal/Dex (18.8 vs 5.6%). Overall, grades 3–4 non-hematologic toxicities were seen in 79.5% of patients with Thal/Dex and 64.2% with dexamethasone alone ($P<0.001$).[24] In another trial, 204 patients were randomly assigned to receive induction treatment with Thal/Dex or with a VAD-like regimen followed by high-dose therapy and ASCT. The very good partial response (VGPR) rate was 34.7% in the Thal/Dex group and 12.6% in the VAD group ($P=0.002$) before ASCT. At 6 months post-transplant, the benefit of Thal/Dex was not further observed with VGPR rates of 44.4% in the Thal/Dex arm and 41.7% in the VAD arm ($P=0.87$).[23] When thalidomide was incorporated into the high-dose therapy followed by ASCT, a higher complete response (CR) rate (62 vs 43%) and improved 5-year event-free survival (56 vs 44%) was observed compared with high-dose therapy without thalidomide.[25] Unfortunately, the 5-year overall survival was similar in both groups ($P=0.9$). In the thalidomide group, a higher rate of thromboembolism (30 vs 17%) and peripheral neuropathy (27 vs 17%) were reported.[25] In the Medical Research Council (MRC) Myeloma IX trial, which has recruited 900 patients, cyclophosphamide-thalidomide- dexamethasone (CTD) was compared with cyclophosphamide- VAD as induction regimen before ASCT. In a preliminary analysis, the CR rate was 20.3% after CTD and 11.7% after cyclophosphamide-VAD; this difference was maintained at 100 days post-ASCT, the CR rate was 58.2% after CTD plus ASCT and 41% after cyclophosphamide-VAD plus ASCT.[26] Thalidomide-based regimens provided superior rates of response when used as induction therapy in comparison with standard treatment. Further studies are needed to assess if this advantage is maintained after ASCT. The efficacy of this combination must be balanced against the greater toxicity and the need for antithrombotic prophylaxis. Patients receiving thalidomide in combination with high-dose steroids or chemotherapy need routine thromboprophylaxis. The presence of a central venous catheter, comorbidities, immobilization as well as the administration of high-dose dexamethasone, multi-agent chemotherapy may significantly increase the risk of thromboembolic events. In these conditions, coumadin (target INR 2–3) or low-molecular weight heparin (equivalent of enoxaparin 40mg once daily) are suggested for the first 4–6 months of therapy. In patients lacking these risk factors aspirin can be used.[27]

Lenalidomide/dexamethasone

The Rev/Dex combination has shown significant activity in a phase II trial conducted at the Mayo Clinic. Thirty-one of 34 newly diagnosed patients (91%) achieved a partial response (PR), including 2 (6%) achieving CR, and 11 (32%) meeting criteria for VGPR.[28] With a longer follow-up, 56% of patients achieved VGPR or better. In the subset of 21 patients receiving Rev/Dex as primary therapy without ASCT, 67% achieved VGPR or better.[29] The

2-year time to progression was 71% for the entire cohort, including 66% of patients who received Rev/Dex without ASCT and 83% of those who received Rev/Dex with ASCT. Approximately, half of the patients experienced grade 3 or higher non-hematologic toxicity.[29] In a recent study, 198 patients were randomly assigned to receive Rev/Dex or dexamethasone alone. The CR rate was significantly higher in the Rev/Dex group (22.4%). The superior response rate translated in a prolonged remission duration: the 1-year PFS was 77% in the Rev/Dex group and 55% in the dexamethasone group (P=0.002). ECOG tested Rev/Dex as administered in the Mayo Phase II trial (and in the regulatory relapsed/refractory myeloma studies) vs Rev/low-dose Dex (40mg dexamethasone once weekly).[30] Results show that toxicity rates are significantly higher with Rev/high-dose Dex compared with Rev/low-dose Dex. Early (first 4 month) mortality rates were low in both groups, 5 and 0.5%, respectively. The early mortality rate in the Rev/low-dose Dex group is probably the lowest reported in any large phase III trial, in which enrollment was not restricted by age or eligibility for stem cell transplantation. The DVT rates observed in this study were also low, making Rev/low-dose Dex one of the safest pretransplant induction regimens for myeloma. Although combinations including low-dose Dex are more appropriate, higher doses of dexamethasone should be considered in the presence of a very aggressive disease, in very young patients, or in the relapse setting. In a phase II trial, Rev/ Dex was combined with clarithromycin (Biaxin), with this BiRD regimen the CR rate was particularly high (38.9%) including a 30.6% of stringent CR (immunofixation negative plus normal free light-chain ratio, plus a negative marrow biopsy by immunohistochemistry).[31] The 2-year PFS was 75.2% both in patients who subsequently received ASCT and those who did not receive any ASCT, and instead received continued BiRD treatment. Cyclophosphamide plus growth factor was used to mobilize stem cells, resulting in a successful harvest in all patients. The number of CD34 cells collected ranged from 4 to 21.5 CD34×10^6/kg.[31] These studies confirm the high efficacy of lenalidomide in the upfront treatment of younger myeloma patients with a better safety profile compared with the parent compound thalidomide. In particular, the combination of lenalidomide with low-dose dexamethasone appears to be the more suitable option in this setting. The incidence of DVT is low with single-agent lenalidomide or Rev/low-dose Dex, but rises markedly when the agent is combined with high-dose dexamethasone. Recommendations for thromboprophylaxis are similar to those discussed above with Thal/Dex; aspirin alone is probably sufficient for patients receiving Rev/low-dose Dex.[27]

Bortezomib-based regimens

Bortezomib is a novel proteasome inhibitor approved by the FDA for the treatment of myeloma in patients who have failed one prior therapy. In newly diagnosed myeloma patients, the combination Bort/Dex showed an overall response rate of 66%, including 21% CR/near CR (nCR) and 10% VGPR.[32] The most common side effects were gastrointestinal symptoms, peripheral neuropathy and fatigue. Peripheral neuropathy was grades 2–3 in 14% of patients. No DVTs and no hematologic toxicity greater than grade 2 were observed. Grade 3 infections were recorded in five patients including three who had herpes zoster infections.[29] To decrease toxicity and to assess efficacy Bort/Dex has been administered in an alternating schedule (bortezomib at 1.3 mg/mq bi-weekly, cycles 1, 3, 5 only) as induction therapy followed by ASCT. This alternating schedule induced a PR rate of 65%, including a CR rate of 12.5% and a VGPR rate of 10%. Toxicity was low with no grades 3–4 peripheral neuropathy or grades 2–4 thrombocytopenia. Chromosome 13 deletion, t(4;14) and t(14;16) did not have a negative impact on response.[33] In a randomized trial, Bort/Dex has been compared with VAD as induction therapy before ASCT.[32] Response to induction showed a significant higher CR plus nCR rate for Bort/Dex (21.3 vs 8.3%), the superiority of Bort/Dex was maintained after ASCT: the CR plus nCR rates were 38 vs 28%. At the interim analysis, the 1-year PFS was 93% for Bort/Dex and 90% for VAD.[34] The

combination bortezomib–dexamethasone–thalidomide has been compared with Thal/Dex in a randomized trial as induction treatment before double ASCT. The CR plus nCR rate was 36% with bortezomib–dexamethasone–thalidomide and 9% with Thal/Dex, and 57% with bortezomib–dexamethasone– thalidomide plus ASCT and 28% with Thal/Dex plus ASCT. Response to bortezomib–dexamethasone–thalidomide was not adversely affected by chromosome 13 deletion or t(4;14).[35] In a phase II study, 100 patients received bortezomib, pegylated– liposomal–doxorubicin and dexamethasone before reduced intensity ASCT (melphalan 100 mg/m^2). After induction with pegylated–liposomal–doxorubicin and dexamethasone, the CR plus nCR rate was 23% and increased to 60% with pegylated–liposomal–doxorubicin and dexamethasone plus reduced intensity ASCT.[36] A novel combination including bortezomib, lenalidomide and dexamethasone has been investigated, it produced high quality responses and was well tolerated in newly diagnosed patients. In 42 patients, this combination induced a PR rate of 98% including 52% VGPRs.[37] The risk of DVT is low with bortezomib (<5%), while peripheral neuropathy can be higher, but alternating regimens significantly reduced this risk. Bortezomib-based regimens may be of value in patients with renal failure, and in those with adverse cytogenetic features such as t(4;14) or deletion 17p13.

New maintenance approaches

The concept of maintenance therapy may open new avenues for new treatment approaches in myeloma. In a large study, patients younger than 65 years were randomly assigned to receive no maintenance, pamidronate, or pamidronate plus thalidomide.[38] The 3-year post-randomization probability of event-free survival (P<0.009) and the 4-year overall survival (P<0.04) were significantly prolonged in patients who received thalidomide. The incidence of thromboembolic events was not significantly different in the three groups. In another study, thalidomide– prednisone was compared with prednisone alone as maintenance therapy after ASCT: the 1-year PFS was 91 vs 69%, and the 2-year overall survival was 90 vs 81%, respectively.[39] In both studies grades 3–4 peripheral neuropathy was significantly more prominent in the thalidomide group than in the controls. More recently, newly diagnosed patients received Thal/Dex as induction, they were then randomly assigned to tandem ASCT or single ASCT followed by thalidomide maintenance.[40] The 3- year PFS was 57% in the double ASCT group and 85% in the single ASCT group, followed by thalidomide maintenance (P=0.02). This study is of particular interest because it shows the advantage of a maintenance approach, even in patients previously treated with Thal/Dex as induction therapy. Bortezomib also showed promising results as a maintenance therapy, suggesting that bortezomib maintenance may favorably impact time to recurrence.[41] Additional studies are needed to determine the role of routine maintenance in myeloma, especially the use of lenalidomide, which has a better safety profile than thalidomide for long-term maintenance.

Patients who are candidates for ASCT should follow a treatment strategy that includes ASCT. However, ASCT can be delayed until relapse if facilities are available to harvest and cryopreserve stem cells early in the disease course. Bortezomib-or lenalidomide-based regimens should be introduced as induction therapy before ASCT, as they significantly increase the VGPR and CR rates before transplantation. Thalidomide should be considered as maintenance after ASCT, specifically in patients who did not reach at least VGPR after single or tandem transplantation. The incorporation of new drugs as induction and maintenance therapy along with ASCT appears to produce VGPR rates slightly superior to those achieved by conventional chemotherapy with new drugs. Randomized trials are needed to directly compare the present best chemotherapeutic approach with best ASCT strategies and guide clinical practice for patients with MM.

Treatment of myeloma in patients not eligible for ASCT

Patients who are not candidates for transplant have been treated for years with standard alkylating agent therapy. In elderly patients, biological age may be quite different from chronological age, for this reason it is difficult to clearly define who is a candidate for ASCT and who is not. The inclusion in an ASCT program should always be considered in the absence of any serious heart, lung, renal and liver dysfunction, while an age limit should be considered and balanced with the biological age. With these limitations it is generally accepted that patients older than 65 years should not receive melphalan 200 mg/m^2 followed by ASCT. In the age group between 65 and 70 years, intermediate-dose melphalan appears a suitable option. In a randomized study, patients, aged 65–70 years, received melphalan 100 mg/m^2 or MP, and the reduced intensity ASCT program was superior to MP.[42] In another study, patients, aged 65–75 years, received melphalan 100 mg/m^2 or MP, ASCT was superior to MP in terms of response rate, but not in terms of PFS and overall survival.[43] In the first study, 22% of patients did not complete the assigned treatment; in the second trial, 37% of patients did not complete it. According to these data, the age of 70 years should be considered as the age limit for intermediate-dose melphalan. Once again, the balance between efficacy and toxicities is extremely important to improve outcome. The discovery of novel therapies, targeting myeloma cells and the bone marrow microenvironment, has changed the treatment paradigm of myeloma therapy, especially for the elderly population.

Thalidomide-based regimens

In younger patients Thal/Dex significantly improves PFS in comparison with high-dose dexamethasone alone.[24] In elderly patients, Thal/Dex was compared with MP in a randomized study. An interim analysis showed a significantly higher response rate in the Thal/Dex group but failed to show any advantage in PFS, while overall survival was superior in the MP group (P=0.02).[44] Patients on Thal/Dex experienced more grades 2–3 neuropathy (25%) and skin toxicity (12%) compared with those on MP (8 vs 3%, respectively). 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. This study raises the question if an alkylating agent is an essential component of drug combinations to improve treatment efficacy. Recently, MP has been combined with thalidomide (MPT) in four different randomized studies. In the first trial, oral MPT was compared with MP in patients aged 60–85 years.[45] The PR rates were 76% in the MPT group and 47.6% in the MP group, nCR or CR rates were 27.9 and 7.2%, respectively. The 2-year event-free survival rates were 54% for MPT and 27% for MP (P=0.0006), with similar 3-year survival rates (P=0.19). In the second study, MPT was compared with MP and with intermediate-dose melphalan (100 mg/m^2) followed by ASCT in patients aged 65–75 years. A higher PR rate was seen in the MPT and in the melphalan 100 mg/m^2 groups, compared with MP (81 vs 76 vs 35%, respectively).[43] Similarly, the CR rates were significantly higher with MPT and intermediate- dose melphalan compared with MP. 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 were 51.6 and 32.2 months, respectively (P=0.001). In the third study, patients aged 75 years and older were randomly assigned to receive MPT or MP plus placebo. The PR rate was 62% in the MPT group and 31% in the MP group, 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).[46] In the fourth study, 362 patients with a mean age of 75 years (range, 49–92) received MPT or MP plus placebo. Results of an interim analysis showed better response rates and time to progression in the MPT group than in the MP group (P<0.03), but did not show any improvement in overall survival.[47] Results from these four randomized studies consistently showed better response rates and remission duration in

patients assigned to MPT than in those receiving MP, but an overall survival benefit was only reported in the two French studies. 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 as the new standard of care for elderly myeloma patients. In all studies, the MPT patients showed a higher incidence of grades 3–4 extra-hematological toxicities compared with the MP regimen, especially neurological adverse events, infections, cardiac toxicity and thromboembolism. Antithrombotic prophylaxis is recommended when using MPT. Recommendations for thromboprophylaxis are similar to those previously discussed with Thal/Dex.[27] 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, 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 should be reduced from 12 cycles to 6 cycles, as prolonged melphalan exposure induces thrombocytopenia that hampers the delivery of subsequent effective salvage regimens.

In the Medical Research Council (MRC) Myeloma IX trial, CTD has been 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.[26] Unfortunately, data on remission durations are not available; if they also are superior to MP, the CTD regimen should be added as an alternative standard frontline approach for elderly patients.

Lenalidomide-based regimens

The Italian group evaluated in a phase I/II trial, dosing, safety and efficacy of melphalan plus prednisone and lenalidomide in newly diagnosed elderly myeloma patients.[48] 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 10mg 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. Grades 3–4 adverse events 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 (6%). 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. This study formed the basis for the ongoing international phase III study comparing MP vs melphalan plus prednisone and lenalidomide. In the near future, the MPT combinations will be challenged by the recent results reported with Len/Dex, using low-dose dexamethasone (40mg on days 1, 8, 15 and 22, every 4 weeks). 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. Recommendations for thromboprophylaxis have already been discussed, with lenalidomide aspirin seems to be the preferred choice in the absence of additional risks of thromboembolism.[27] 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 always be applied in the presence of severe neutropenia despite granulocyte-colony stimulating factor.

Bortezomib based-regimens

The Spanish cooperative group conducted a large phase I/II trial of bortezomib, melphalan and prednisone (MPV).[49] The association showed encouraging results: PR rate was 89%, including 32% immunofixation-negative CR, half of them achieved immunophenotypic remission (no detectable plasma cells at 10^{-4} to 10^{-5} sensitivity). PFS at 16 months for VMP patients was significantly prolonged in comparison with historical controls treated with MP only (91 vs 66%), similarly overall survival at 16 months was improved (90 vs 62%). Interestingly, response rate, PFS and overall survival were similar among patients with or without chromosome 13 deletion or IgH translocations. Grades 3–4 adverse events observed with MPV were mainly thrombocytopenia, neutropenia, peripheral neuropathy, infections and diarrhea. The treatment appeared more toxic in patients older then 75 years. Bortezomib can induce transient thrombocytopenia and peripheral neuropathy. 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. Bortezomib may enhance the incidence of infections, in particular, herpes zoster reactivation, and prophylactic antiviral medications are highly recommended. These data have recently been confirmed in a large randomized trial comparing MPV with MP and have provided the basis for MPV as an alternative standard of care for elderly patients.[50]

The efficacy of these new regimens should be balanced against their higher toxicities: in the presence of high risk of thromboembolism, MPV could be the preferred option; in the presence of peripheral neuropathy, MPR should be considered; in patients with renal insufficiency, MPV is better tolerated; and MPT should be considered if costs are a concern. Oral treatment should also be balanced vs intravenous treatment, as the latter is more invasive.

Management of bone disease

Bone lytic disease is the most frequent complication of myeloma. Pamidronate and zoledronic acid are the cornerstone for the treatment of lytic disease in myeloma. Concerns have risen during the last years about their renal side effects and osteonecrosis of the jaw, a complication which is related to long-term use of potent biphosphonates.[51] The discovery of novel agents with a beneficial effect on abnormal bone remodeling of myeloma is highly expected. Bortezomib has special effects on myeloma bone metabolism. Bortezomib increased the number of osteoblastic cells/mm^2 and the Runx2/Cbfa1-positive osteoblasts in bone biopsies of responding myeloma patients, but not in those who did not respond.[52] In addition to promoting bone formation, bortezomib has been reported to affect osteoclast differentiation and function. Bortezomib was shown to inhibit osteoclast differentiation in a dose- and time-dependent manner, as well as inhibit the bone resorption activity of osteoclasts.[53] The results of these studies indicate that bortezomib may be the first agent that combines potent antimyeloma activity with potential beneficial effects on bone (Tables 1–3).

Conclusions

High-dose melphalan followed by ASCT in younger patients and oral MPT or MPV in elderly patients are the standard of care for the frontline therapy of myeloma. Survival after transplant appears to be related to the achievement of CR or VGPR. Improved response rate after induction treatment, before transplant, could translate to better results after high-dose therapy with prolonged survival. In younger patients, combinations incorporating thalidomide or lenalidomide or bortezomib significantly increase the pretransplant CR plus VGPR rate before high-dose melphalan and autologous transplantation. These combinations may further improve the CR plus VGPR rate achieved after transplant. A reasonable

alternative approach is to collect stem cell at diagnosis and leave the ASCT option for relapse. Both approaches need the evidence of efficacy from the ongoing prospective randomized studies. These evidences should always include at least data on PFS advantage. If survival improvement represents the ultimate goal, response advantage is not adequate, by itself, to define treatment efficacy.

Cytogenetic abnormalities, such as chromosome 13 deletion or t(4;14), are considered negative prognostic factors. Unfortunately, most of the studies reported to date have not prospectively stratified patients based on cytogenetic abnormalities, making a firm conclusion difficult. In a small cohort of patients receiving bortezomib or lenalidomide, the PFS of patients with deletion of chromosome 13 or chromosomal translocation (4;14) was not significantly different from those who did not show such abnormalities. It must however, be mentioned that irrespective of cytogenetic 'risk profile,' MM remains incurable. To determine the optimal regimen for each individual patient based on a cytogenetically adapted strategy, comprehensive study and long-term follow-up is required.

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Table 1

Treatment schema

Regimen	*Usual dosing schedule*
Transplant candidates	
Thalidomide/ dexamethasone[a]	Oral thalidomide 100–200mg on days 1–28 Oral dexamethasone 40mg on days 1, 8, 15, and 22, every 28 days Repeated every 4 weeks for four cycles as pretransplant induction therapy; or continued for up to 1 year if used as primary therapy
Lenalidomide/ dexamethasone	Oral lenalidomide 25mg on days 1–21, every 28 days Oral dexamethasone 40mg on days 1, 8, 15, and 22, every 28 days Repeated every 4 weeks for two cycles as pretransplant induction therapy; or continued until progression if used as primary therapy
Bortezomib/ dexamethasone	Intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 Oral dexamethasone 40mg on days 1–4, 9–12 Reduce dexamethasone to days 1–4 only after first two cycles Repeated every 3 weeks for 2–4 cycles as pretransplant induction therapy
Bortezomib/ thalidomide/ dexamethasone[a]	Intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 Oral thalidomide 200 mg, days 1–21 Dexamethasone 20mg on the day of and the day after bortezomib Repeated every 3 weeks for three cycles as pretransplant induction therapy
Bortezomib/pegylated liposomal doxorubicin/ dexamethasone	Intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 Pegylated liposomal doxorubicin 30 mg/m^2 on day 4 Dexamethasone 40mg on days 1–11, and 15–18 for cycle 1 and days 1–4 for cycles 2–4
Cyclophosphamide/ thalidomide/ dexamethasone	Cyclophosphamide 500mg post-operative on days 1, 8 and 15 Thalidomide 100–200 mg/day Dexamethasone 40 mg/day post-operative on days 1–4, 12–15 every 3 weeks
Non-transplant candidates	
Melphalan/prednisone/ thalidomide[b]	Oral melphalan 0.25 mg/kg on days 1–4 Oral prednisone 2mg/kg on days 1–4 Oral thalidomide 100–200mg on days 1–28 Repeated every 6 weeks for 12 cycles
Melphalan/prednisone/ bortezomib	Oral melphalan 9 mg/m^2 on days 1–4 Oral prednisone 60 mg/m^2 on days 1–4 Intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29 and 32 Repeat every 42 days for four cycles followed by maintenance therapy Oral melphalan 9 mg/m^2 on days 1–4 Oral prednisone 60 mg/m^2 on days 1–4 Intravenous bortezomib 1.3 mg/m^2 on days 1, 8, 15 and 22 Repeated every 35 days for five cycles
Melphalan/prednisone/ lenalidomide	Oral melphalan from 0.18 mg/kg on days 1–4 Oral prednisone 2mg/kg on days 1–4 Oral lenalidomide from 10mg on days 1–21 Repeated every 28 days for 9 monthly cycles

[a] Dexamethasone dose listed is lower than used in trial.

[b] Thalidomide dose listed is lower than used in trial.

Table 2

Efficacy of regimens used as frontline treatment in multiple myeloma

Therapy	*No. of patients*	*≥PR (%)*	*≥VGPR (%)*	*Progression-free survival*	*Overall survival*	*References*
Transplant candidates						
Thal/Dex	235	63	43.8	14.9 months	68% @ 2 years	[24]
ASCT-T	323	ND	ND	56% @ 5 years	65% @ 5 years	[25]
Rev/Dex	34	91	38	74% @ 2 years	91% @ 2 years	[28]
BiRD	72	90	73	75% @ 2 years	ND	[31]
Bort/Dex	52	66	31	ND	ND	[32]
PAD	65	97.1	50	83% @ 2 years	92% @ 2 years	[36]
Non-transplant candidates						
MPT	129	76	36	54% @ 2 years	80% @ 3 years	[45]
MPT	125	76	47	27.5 months	51.6 months	[43]
MPR	54	81	47	80% @ 2 years	91% @ 2 years	[48]
MPV	60	89	ND	65% @ 2 years	86% @ 2 years	[49]

Abbreviations: ASCT-T, autologous stem cell transplantation+thalidomide; BiRD, biaxin+lenalidomide+dexamethasone; Bort/Dex, bortezomib+-dexamethasone; MPR, melphalan+prednisone +lenalidomide; MPT, melphalan+prednisone+thalidomide; MPV, melphalan+prednisone+bortezomib; ND, not determined; PAD, bortezomib+pegylated-lyposomal-doxorubicin+dexamethasone; PR, partial response; Rev/Dex, lenalidomide+dexamethasone; Thal/Dex, thalidomide+dexamethasone; VGPR, very good partial response; VTD, bortezomib+thalidomide+dexamethasone.

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Table 3

Safety of regimens used as frontline treatment in multiple myeloma

Therapy	*Peripheral-neuropathy grades 3–4 (%)*	*DVT/embolism grades 3–4 (%)*	*Neutropenia grades 3–4 (%)*	*Thrombocytopenia grades 3–4 (%)*	*Infection grades 3–4 (%)*	*References*
Transplant candidates						
Thal/Dex	3.4	11.5	3.4	ND	7.3	24
ASCT-T	27	30	94	ND	ND	25
Rev/Dex	0	3	12	0	6	28
BiRD	4	9	19	22	9	31
Bort/Dex	6	0	ND	ND	9	32
PAD	16	4	8.1	13.5	10.8	36
Non-transplant candidates						
MPT	8	9	16	3	10	45
MPT	6	12	48	14	13	43
MPR	0	4.8	52	23	9.5	48
MPV	17	0	43	51	16	49

Abbreviations: ASCT-T, autologous stem cell transplantation+thalidomide; BiRD, biaxin+lenalidomide+dexamethasone; Bort/Dex, bortezomib+ dexamethasone; MPR, melphalan+prednisone +lenalidomide; MPT, melphalan+prednisone+thalidomide; MPV, melphalan+prednisone+bortezomib; ND, not determined; PAD, bortezomib+pegylated-lyposomal-doxorubicin+dexamethasone; Rev/Dex, lenalidomide+dexamethasone; Thal/ Dex, thalidomide+dexamethasone; VTD, bortezomib+thalidomide+dexamethasone.