Introduction

Multiple myeloma accounts for approximately 10% of hematologic malignancies, the frequency is constantly increasing due to aging of the general population.1,2 Recently, novel agents, such as thalidomide, bortezomib and lenalidomide have shown significant activity in multiple myeloma. Combinations of these agents with steroids, alkylating agents or anthracyclines have significantly improved response rate and progression-free survival (PFS). In elderly patients, older than 65 years, oral melphalan and prednisone (MP) has been combined with thalidomide or bortezomib significantly improving response rate and PFS.

Prognostic factors

The clinical course of multiple myeloma is quite heterogeneous. The International staging system (ISS) provides a simple, powerful and reproducible three-stage classification: stage I is characterized by β2-microglobulin less than 3.5 mg/L plus serum albumin ≥3.5 g/dL 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 β2-microglobulin ≥5.5 mg/L with a median survival of 29 months.3 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.5 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 FISH together with measurements of serum β2-microglobulin and LDH.7

Treatment

There is little evidence that early treatment of patients with asymptomatic multiple myeloma 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 smouldering myeloma.
for years with standard alkylating agent therapy. 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 biologic age. With these limitations it is generally accepted that patients older than 65 years should not receive melphalan 200 mg/m² followed by ASCT. In the age group between 65-70 years, intermediate dose-melphalan appears a suitable option. In a randomized study, patients, aged 65-70 years, received melphalan 100 mg/m² or MP, and the reduced intensity ASCT program was superior to MP. In another study, patients, aged 65-75 years, received melphalan 100 mg/m² or MP, ASCT was superior to MP in terms of response rate, but not in terms of PFS and overall survival. 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.

**Thalidomide-based regimens**

In younger patients Thal/Dex significantly improves PFS in comparison with high-dose dexamethasone alone. 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). Patients on Thal/Dex experienced more grade 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 4 different randomized studies. In the first trial, oral MPT was compared with MP in patients aged 60-85 years. 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/m²) followed by ASCT in patients aged 65-75 years. A higher PR rate was seen in the MPT and in the melphalan 100 mg/m² groups, compared with MP (81% vs. 76% vs. 35%, respectively). 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 months 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). 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 TTP in the MPT group than in the MP group (p<0.03), but did not show any improvement in overall survival. 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.

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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 grade 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.15 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 grade 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, since 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.16

**Lenalidomide-based regimens**

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.17 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. 85% 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. Grade 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 versus MPR. In the near future, the MPT combinations will be challenged by the recent results reported with Len/Dex, using low-dose dexamethasone (40 mg 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 absence of additional risks of thromboembolism.15 The addition of granulocyte-colony stimulating factor (G-CSF) is recommended in case of neutropenia, and melphalan dose reduction (from 0.18 mg/kg to 0.13 mg/kg) should always be applied in the presence of severe neutropenia despite G-CSF.

**Bortezomib-based regimens**

The Spanish cooperative group conducted a large phase I/II trial of bortezomib, melphalan, and prednisone (MPV).18 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. Grade 3-4 adverse events observed with MPV were mainly thrombocytopenia, neutropenia, peripheral neuropathy, infections and diarrhea. The treatment appeared more toxic in patients older than 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.19

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 versus intravenous treatment as the latter is more invasive.

References

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