Advances in the treatment of multiple myeloma

Meletios A. Dimopoulos, Evangelos Terpos

Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece

Introduction

Treatment for multiple myeloma (MM) has considerably improved in the past decade. However, MM continues to be an incurable haematological malignancy that causes most patients to eventually relapse and die of their disease. Thus, efforts to further improve response rates and survival in myeloma patients are urgently needed.

Front-line therapy for patients who are eligible for autologous stem cell transplantation

Induction therapy using 3–4 cycles of a novel agent-based regimen followed by high-dose melphalan and autologous stem cell transplantation (ASCT) is the standard of care for patients who are younger than 66 years of age with no comorbidities or even for elderly patients (up to the age of 70 years) with very good performance status. The use of thalidomide plus dexamethasone (TD) has been extensively studied and several studies have shown an objective response rate (ORR) of between 48 and 80%, including complete response (CR) rates of 4–16%. The combination of TD with adriamycin (TAD) also proved to be superior to VAD as an induction regimen regarding ORR, overall survival (OS) and progression-free survival (PFS) [1]. Bortezomib-based regimens have also produced very good results in terms of both ORR and survival as induction treatment pre-ASCT [2]. In two large randomised trials the ORR ranges from 80% pre-ASCT to 90% post-ASCT with 30–40% CR plus near CR (nCR) rates. In a recent randomised trial (the EVOLUTION trial) the combination of bortezomib, cyclophosphamide (given weekly in a three-week cycle) and dexamethasone (VCD modified) has produced the more promising results in terms of increased efficacy and reduced toxicity (in comparison to VCD, VRD or VRCD). Lenalidomide has also been evaluated in the frontline setting and its combination with low-dose dexamethasone (Rd) has shown a higher probability of one-year OS compared with the combination of lenalidomide with high-dose dexamethasone (RD, 96% vs. 87%, $P = 0.0002$) [3]. A retrospective analysis that compared RD with TD showed that RD patients had longer time to progression (TTP), PFS and OS than TD patients [4]. Finally, a triple combination with bortezomib, thalidomide, and dexamethasone (VTD) has proven to be superior to VD in three recent randomised studies with regard to ORR but not OS.

Front-line therapy for patients who are not eligible for autologous stem cell transplantation

The standard of care for these patients is the combination of melphalan/prednisone (MP) with either thalidomide (MPT) or bortezomib (MPV). In a recent meta-analysis, which included six randomised studies with 1682 patients, and compared MPT with MP, MPT improved PFS (20.4 vs. 14.9 months, $P = 0.001$) but not OS (39.3 vs. 32.7 months, $P = 0.085$). MPV is the second standard of care in elderly patients. Compared with MP, MPV produced a significant improvement in ORR (71% vs. 35%), CR rate (30% vs. 4%; $P < 0.001$), TTP (24 vs. 16.6 months; $P < 0.001$), and OS at three years (72% vs. 59%, $P = 0.0032$). This superiority was also recorded in patients aged >75 years and in patients with moderate renal impairment [5]. In a UK trial, the CTD regimen was compared with standard MP in 900 patients. CTD produced higher ORR (82% vs. 49%) and CR rates (23% vs. 6%) than MP did. Another regimen, the combination of melphalan, prednisone, and lenalidomide (MPR) has been investigated in a phase III study with three arms. MPR or MP was given for nine cycles followed by placebo until progression, while in the third arm MPR was followed by R maintenance until progression. MPR-R, compared with MP, resulted in a higher ORR (77% vs. 50%, $P < 0.001$) as well as higher rates of CR (16% vs. 4%, $P < 0.001$) and a very good partial response (VGPR) or better (32% vs. 12%, $P < 0.001$). Overall, MPR-R reduced the risk of disease progression by 58% compared with MP with a higher two-year PFS rate (55% vs. 16%).

A landmark analysis comparing MPR-R and MPR initiated at the beginning of cycle 10 demonstrated that maintenance lenalidomide resulted in a 69% reduced risk of progression compared with placebo. In addition, regardless of induction response ($\geqslant$ VGPR or PR), patients who received maintenance lenalidomide had longer PFS compared with placebo.

Treatment of patients with relapsed/refractory myeloma

Bortezomib-based combinations produce ORR of 40–50% and TTP of 6–9 months [6], while RD produces ORR of 60% and TTP of 13.5 months [7]. Major toxicities with bortezomib include peripheral neuropathy, thrombocytopenia, neutropenia, and gastrointestinal adverse events, while the main toxicities reported with RD include neutropenia, thrombocytopenia, venous thromboembolism and infections. Lenalidomide is also very effective in patients previously treated with thalidomide. The efficacy and safety of thalidomide for relapsed or refractory multiple myeloma has not been evaluated in the context of large, prospective, randomised trials. In a meta-analysis of nine published studies, thalidomide, at median doses of 200–800 mg per day, produced ORR of 28%, including a CR rate of 1.6%. Peripheral neuropathy varied from 12 to 44%, possibly impacted by the short median follow-up (9–29 months). Incidence of pooled venous thromboembolism was 2.7% and discontinuation due to intolerance was 15%. Finally, the combination of three or four agents, including two novel agents, has been used in the relapsed/refractory setting with high ORR: the VRD regimen produced an ORR of 67%, the VMDT 66%, and the RMPT 75%. Several studies are on-going in an effort to reveal the more appropriate therapy for relapsed/refractory patients. Furthermore, novel drugs, including proteasome inhibitors (carfilzomib, salinosporamide), IMiDs (pomalidomide), alkylators (bendamustine), AKT inhibitors (perifosine, rapamycin), heat-shock-protein inhibitors (tanespimycin), and histone deacetylase inhibitors (vorinostat, panobinostat) have been entered in phase II/III trials and the results will reveal their role in the management of relapsed/refractory myeloma [1].

Maintenance therapy post-ASCT in myeloma

Thalidomide has been found in three randomised studies to prolong PFS, while bortezomib maintenance has also shown increased ORR and PFS in several small studies. Lenalidomide is an attractive alternative to thalidomide because of the lack of neurological toxicity. Two independent randomised trials have recently shown a significantly longer PFS for patients randomised to lenalidomide maintenance (5–15 mg per day) in comparison to the placebo group after a single or double ASCT. In the French study (IFM 2005–02), after a median follow-up of 34 months, the median PFS was 42 versus 24 months for the lenalidomide and placebo arms respectively ($P < 10^{-8}$). This has not yet been translated into an OS benefit (five-year OS probability: 81% for both arms), although the highly significant p value of PFS suggests that an OS benefit may become evident with a longer follow-up period. In the US-based trial (CALGB-100104), after a median follow-up of 17.5 months, the results for median PFS were similar to those of the French study: 43 versus 21 months for the lenalidomide and placebo arms respectively ($P < 10^{-4}$), but in the recent IMW a significant increase in OD in the lenalidomide arm was reported ($P = 0.05$). An increased incidence of second primary malignancies, around 7%, has recently been reported. While a concerted effort is needed to better define the underlying mechanisms and identify risk factors, the optimal role and duration of lenalidomide maintenance therapy needs to be tested in future clinical trials.

Conflict of interest statement

M.A. Dimopoulos has received honoraria from Celgene, Janssen-Cilag, Ortho Biotech, Novartis and Onyx. E. Terpos has received honoraria from Celgene, Janssen-Cilag, Novartis and Amgen.

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