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REVIEW

# First line therapy for patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplantation: a systematic review and meta-analysis (hemo-oncolgroup study)

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## Abstract

**Background:** Patients not eligible for stem cell transplantation (SCT) have been treated with melphalan (M) plus prednisone (P); however, the standard of care has shifted to MP plus thalidomide (T) due to a greater survival benefit. Bortezomib (B) and lenalidomide have also emerged as effective agents. **Methods:** Randomized clinical trials (RCTs) that compared MP to any other regimen were identified from the databases of Cochrane Library, PubMed, LILACS, EMBASE and Scirus. **Results:** Twenty-two trials were included from 2159 potential eligible references. MP *vs.* M plus dexamethasone (MD): (3 RCTs) MD was superior in partial response (PR) rate and non-hematological toxicity. MP *vs.* T-based regimens: (4 RCTs) significant differences favoring T-based regimens in complete response (CR) rate, partial response (PR) rate, and progression-free survival (PFS). MP *vs.* B based regimens: (1 RCT) significant differences in overall survival (OS) , time to progression (TTP), CR and PR rate favored B-based regimens according to the European Group for Blood and Marrow Transplantation (EBMT) criteria. MP *vs.* chemotherapy regimens without M: (3 RCTs) A significantly higher number of patients treated with BP achieved a CR. TTP was also significantly longer in BP-treated patients ($p < 0.02$). MP *vs.* other polychemotherapy regimens: (13 RCTs) No significant differences in PR, OS, hematological or other type of toxicity were observed between MP and the other chemotherapy regimens. **Conclusions:** Symptomatic multiple myeloma patients ineligible for SCT should receive as first-line treatment a combination of MP plus B or T; these regimens are associated with improved outcome but greater toxicity compared to MP alone. More homogeneous clinical trials using a cytogenetic risk approach are required.

**Keywords:** drug therapy; meta-analysis; multiple myeloma; randomized controlled trial; systematic review.

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## INTRODUCTION

Multiple myeloma (MM) is a clonal malignancy characterized by proliferation of abnormal plasma cells that impair hematopoiesis, activate bone resorption, and secrete a monoclonal paraprotein in serum and urine[1]. MM accounts for about 1% of human neoplasms, almost 2% of cancer-related deaths, and 12% to 15% of hematological malignancies[2]. MM patients with symptomatic disease are usually considered candidates for chemotherapy-based treatment[3]: those who are eligible for high-dose therapy followed by stem cell transplantation (SCT), and those who are ineligible for SCT[4]. Criteria for deciding on eligibility for SCT generally include age, performance status (PS), and co-morbid conditions[5]. There is some variability in these parameters and how they are applied, since studies examining SCT have been carried out with heterogeneous criteria. For example, initial studies tended to include patients younger than 65 years of age, while more recent trials suggest that SCT is safe in a selected group of patients over 70[6]. On the other hand, since patients with poor-risk chromosomal features have a short progression free survival (PFS) after SCT, even younger patients with these alterations may not be candidates for transplantation[7].

Since the 1960s, the standard of care for patients ineligible for SCT has been melphalan plus prednisone (MP)[8]. However, there have been different treatment options ex-

plored in RCTs since this decade, that include dexamethasone (D) alone, melphalan plus dexamethasone (MD)[9-12], thalidomide added to MP (MPT)[12-14], and bortezomib in combination with MP (BMP)[15-18]. It is important to create an evidence-based medical criteria for making clinical choices in order to give to the patients the best treatment option, based on safety and efficacy of each treatment strategy.

In this systematic review and meta-analysis, we assess the evidence from randomized clinical trials (RCTs) comparing MP to any other regimen in order to determine the efficacy and toxicity of different systemic treatments for newly diagnosed MM patients ineligible for SCT.

## METHODS

### Literature search

Relevant randomized controlled trials (RCTs) were identified from the Cochrane Central Register of Controlled Trials (The Cochrane Library 2008, Issue 3), PubMed (1966 to April 2009), LILACS (1982 to December 2008), EMBASE (1980 to December 2008) and Scirus (December 2008). A search strategy to locate studies on newly diagnosed MM patients ineligible for SCT was structured and adapted according to each electronic database (Appendix A). Ongoing trials were searched using the following web sites: the International Clinical Trials Registry Platform (ICTRP) search portal (http://www.who.int/trialsearch/Default.aspx); the meta-Register of Controlled Trials (www.controlled-trials.com); and http://clinicaltrials.gov/. Eligible RCTs were included regardless of the language of publication. We also scanned bibliographies of relevant studies for possible references to additional RCTs and searched the abstracts from the annual meetings of the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH) and the European Society of Medical Oncology (ESMO) from 1980 onwards. Pharmaceutical firms and authors were also contacted when deemed necessary.

### Study selection

Only RCTs comparing MP *versus* any other regimen for newly diagnosed MM patients ineligible for SCT were considered in this systematic review. We included all doses and treatment regimens whether as single agents or in combination therapy. Quasi-randomized and non-randomized controlled studies were excluded. Trials were included based on the independent decisions of at least two reviewers, and any disagreements were resolved by discussion, with referral to a third reviewer if necessary.

### Data extraction

At least two reviewers independently extracted the relevant data using a pre-designed data extraction form. Data included the year of publication, patient population, number of patients (by intent-to-treat [ITT] analysis), sample size, sociodemographic details, treatment details (i.e. drug, dose, duration), clinical outcomes and main adverse events.

### Definitions and outcomes

The primary outcomes were ORR, PFS and OS. In addition, we also considered TTP and the rate of adverse events as secondary outcomes (following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0); no further searches for other types of studies were attempted to identify adverse events[19-20].

### Risk of bias assessment

A risk of bias evaluation of each RCT was done to include details of randomization, allocation concealment, blinded assessment, incomplete outcome data, selective outcome reporting and other issues, in accordance with the guidelines contained in the Cochrane Collaboration handbook[21]. The tool for assessing risk of bias in each RCT comprises a description and a judgment for each entry in a risk-of-bias table. The judgment for each entry involves answering a question, with 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating either lack of information or uncertainty over the potential for bias. A study should be considered has having a low risk of bias if all key domains were judged as 'Yes' and with unclear risk if the reviewers answered 'Unclear' for one or more key domains[21-22].

### Description of studies

Of 2159 RCTs screened, 106 assessed the efficacy in terms of OS and PFS and the toxicity of systemic treatment of newly diagnosed MM patients ineligible for SCT (Figure 1)[13,14,18,23-129]. Of these, 81 references were excluded either because they were non-randomized trials or because they did not compare MP *versus* another regimen[45-129] (Figure 1). Of the 25 RCTs meeting the inclusion criteria[13-14,18,23-44], two[14,43] were an update of other studies[13,18] and two were published only as abstracts[41-42]. The main characteristics of the 25 included studies are detailed in Annex 1.

Only two studies were not open[42-44] and three had a low risk of bias[13,34,39]. Overall, 19 RCTs were judged to have an unclear risk of bias, mainly because the description of the method used to generate the allocation sequence and/or to conceal the allocation was unclear (Annex 2). The majority of RCTs did not calculate the sample size, which was a potential source of imprecision.

### Statistical analysis

To estimate differences between treatments, we pooled the results of RCTs comparing similar treatments and controls and then calculated a weighted treatment effect across the studies. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes and weighted mean differences (WMD) with 95% CIs for continuous outcomes. The generic inverse variance by logHR and SE (logHR) was used for time-to-event data[21-22]. For the pooled analysis, we calculated the $I^2$ statistic, which describes the percentage of total variation across studies caused by heterogeneity[21]. Low, moderate, and high levels of heterogeneity correspond approximately to $I^2$ values of 25%, 50% and 75%, respectively[21]. We used the fixed effect model when the $I^2$ was < 49.9% and the random-effect model when $I^2$ was ≥ 50%. Available information was summarized and based on ITT whenever possible. A qualitative description of adverse effects was provided whenever possible. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with Review Manager version 5.0 (RevMan, The Cochrane Collaboration).

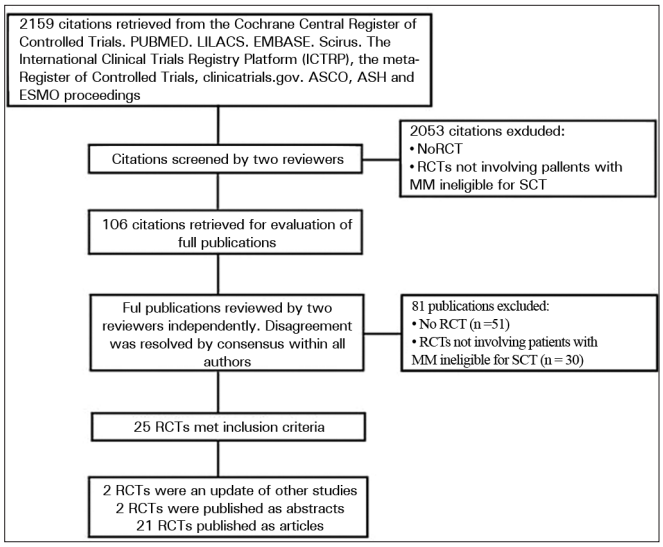


**Figure 1.** Flow chart for inclusion and exclusion of studies.

## RESULTS

Tables 1, 2 and 3 shows the main findings for OS, response rate, hematological and non-hematological toxicity in RCTs included in the review.

### MP *versus* MD

Three RCTs evaluating MP *versus* MD were included in the analysis[29,31,39]. Although no significant differences were observed between the two treatments in OS (3 RCTs HR, 0.95; 95%CI, 0.82-1.10; $I^2$, 0%)[29,31,39], CR rate (2 RCTs, 389 patients: RR, 0.35; 95%CI, 0.10-1.25; $I^2$, 0%) or hematological toxicity (2 RCTs, 415 patients: RR, 1.15; 95%CI, 0.77-1.74; $I^2$, 24%)[29,31], a higher PR rate (3 RCTs, 855 patients: RR, 1.54; 95%CI, 1.32-1.80; $I^2$, 17%)[29,31,39] with fewer non-hematological toxicities (2 RCTs, 415 patients: RR, 2.15; 95%CI, 1.36-3.41; $I^2$, 46%)[29,31] was observed in patients treated with MD. However, thrombocytopenia was lower in the MD group in one trial (RR, 0.70; 95%CI, 0.54-0.91)[39]. A non-significant trend towards a higher rate of severe bacterial infections was also found in patients treated with MD in one RCT (RR 1.90; 95%CI, 0.98-3.65)[29]. However, two studies reported that non-hematological toxicity was significantly higher in patients treated with MD, mainly due to infections and hyperglycemia[31,39]. One RCT found that PFS was 21.1 *versus* 22.9 months (MD - HR 1.80 95%CI -2.27 to -1.33; $p < 0.01$)[29]; 15.9 *versus* 23.3 months ($p = 0.35$)[31]; and 1.8 *versus* 1.9 years (HR 0.88 95%CI 0.72-1.07; $p = 0.2$) for induction therapy and 2.8 *versus* 2.1 years (HR 0.61 95%CI 0.47-0.79; $p = 0.0002$) for maintenance therapy[39].

### MP *versus* MPT

Seven studies comparing MP and MPT were identified[13-14,29,34,41-42,44], one of which was an update of a previously published study[14]. Another trial did not report the number of participants randomized and analyzed in each arm and was excluded from the analysis[42]. Anon-significant trend towards longer OS was observed in MPT-treated patients when 4 RCTs were pooled (HR, 0.80; 95%CI, 0.53-1.20; $I^2$, 84%); however, the patients included in the four trials were very heterogeneous, which may have skewed the results[13,29,34,44] (Figure 2A). When one RCT was excluded[34], a significant difference in OS

**Table 1.** Main findings for overall survival.

| References | Intervention | Comparison | Hazard ratio (95%CI) | Heterogeneity $I^2$ |
|---|---|---|---|---|
| 18,33,39 | Combination regimen (MP/MD) + Thalidomide** | MP | 0.79 (0.66-0.96) | 86% |
| 23 | BMP** | MP | 0.61 (0.42-0.89) | - |
| 34,36,44 | MD | MP | 0.95 (0.82-1.10) | 0% |
| 42 | Chemotherapy regimens without melphalan (prednisone + bendamustine) | MP | 1.0 (0.58-1.73) | - |
| 28-33,35,37,38,40,41,43,45 | More aggressive chemotherapy regimens | MP | 0.95 (0.88-1.03) | 0% |

BMP: Bortezomib/Melphalan/Prednisone; MP: Melphalan/Prednisone; MD: Melphalan/Dexamethasone. * Hazard Ratio and 95% confidence intervals (CI) were calculated using the generic inverse variance. ** Favoring this intervention.

**Table 2.** Main findings for response to therapy.

| References | Intervention | Comparison | Type of response | Relative risk (95%CI)* | Heterogeneity $I^2$ |
|---|---|---|---|---|---|
| 18,33,39,46 | Combination regimen (MP/MD) + Thalidomide** | MP | Complete response<br>At least partial response | 3.44 (1.86-6.39)<br>1.67 (1.28-2.17) | 53%<br>74% |
| 23 | BMP | MP | Complete response<br>At least partial response | 8.35 (4.68-14.89)<br>1.30 (1.06-1.59) | -<br>- |
| 34,36,44 | MD** | MP | Complete response<br>At least partial response | 0.35 (0.10-1.25)<br>1.54 (1.32-1.80) | 0%<br>17% |
| 34,42,45 | Chemotherapy regimens without melphalan | MP | Complete response | 0.99 (0.10-9.46) | 78% |
| 28-33,35,37,38,40,41,43,45 | More aggressive chemotherapy regimens | MP | Complete response<br>At least partial response | 1.06 (0.49-2.41) | 75% |

BMP: Bortezomib/Melphalan/Prednisone; MP: Melphalan/Prednisone; MD: Melphalan/Dexamethasone. * Relative Risk and 95% confidence intervals (CI) for dichotomous primary outcomes were calculated by the Mantel-Haenszel fixed-effects model when $I^2 < 50\%$. Relative Risk and 95% confidence intervals (CI) for dichotomous primary outcomes were calculated by the Mantel-Haenszel random-effects model when $I^2 > 50\%$. ** Favoring this intervention.

**Table 3.** Main findings for hematological and non-hematological toxicity (grade 3-4).

| References | Intervention | Comparison | RR (95%CI)* | Heterogeneity $I^2$ |
|---|---|---|---|---|
| **Hematological toxicity** | | | | |
| 18,33,39 | Combination regimen (MP/MD) + Thalidomide** | MP | 0.79 (0.19-3.29) | 97% |
| 23 | BMP | MP | 1.11 (0.86-1.44) | - |
| 34,36 | MD | MP | 1.15 (0.77-1.74) | 24% |
| 32,34,35,40 | More aggressive chemotherapy regimens | MP | 1.23 (0.85-1.80) | 88% |
| **Non-hematological toxicity** | | | | |
| 18,33,39 | Combination regimen (MP/MD) + Thalidomide** | MP | 2.14 (1.80-2.55) | 0% |
| 23 | BMP | MP | 1.27 (0.68-2.37) (data for overall grade 3-4 toxicity) | - |
| 34,36 | MD** | MP | 2.15 (1.36-3.41) | 46% |
| 32,34,37 | More aggressive chemotherapy regimens | MP | 1.46 (0.90-2.37) | 91% |

BMP: Bortezomib/Melphalan/Prednisone; MP: Melphalan/Prednisone; MD: Melphalan/Dexhamethasone. * Relative Risk and 95% confidence intervals (CI) for dichotomous primary outcomes were calculated by the Mantel-Haenszel fixed-effects model when $I^2 < 50\%$. Relative Risk and 95% confidence intervals (CI) for dichotomous primary outcomes were calculated by the Mantel-Haenszel random-effects model when $I^2 > 50\%$. ** Favoring this intervention.

favoring MPT was found (HR, 0.80; 95%CI, 0.53-1.22; $I^2$, 0%). When five RCTs, with a total of 1335 patients, were pooled, higher CR (RR, 3.75; 95%CI, 2.07-6.77; $I^2$, 40%) (Figure 2B) and PR rates (RR, 1.72; 95%CI, 1.37-2.15; $I^2$, 70%) were attained with MPT[13,29,34,41,44].

In four RCTs, median PFS was significantly higher in patients treated with MPT: (HR, 0.51; 95%CI, 0.35-0.75)[13], 17.8 *versus* 27.5 months (HR, 0·45; $p < 0.0001$)[29], 24.1 *versus* 18.5 months (HR 0.62; $p = 0.001$)[44], and 10 *versus* 13 months ($p < 0.02$)[41]. Conversely, in a fifth trial, median PFS was 16.7 and 20.7 months for the TD and MP groups, respectively (HR, 1.30; 95%CI, 0.95-1.78)[34]. The proportion of patients without progressive disease at 12 and 24 months was 59% (95%CI, 51-68%) and 41% (95%CI, 33-51%) for those treated with TD and 63% (95%CI, 55-72%) and 48% (95%CI, 40-58%) for those treated with MP[34].

In three RCTs with a total of 860 patients, no significant differences were found in grade 3-4 hematological toxicities (RR, 0.79; 95%CI, 0.19- 3.29; $I^2$, 97%); however, greater differences were observed in non-hematological toxicities (RR, 2.14; 95%CI, 1.80-2.55; $I^2$, 0%)[13,29,34]. Thrombosis/embolism was significantly higher in the MPT group in four RCTs with 1069 patients (RR, 2.69; 95%CI, 1.68-4.33; $I^2$, 3%)[13,29,34,44]. However, no significant difference was found between the two treatment groups in the two RCTs, with 523 patients, with available data on pulmonary embolism (RR, 1.68; 95%CI, 0.30-9.35; $I^2$, 29%)[13,34] (Figure 3A). Finally, in four trials with a total of 1069 patients, peripheral neuropathy was significantly higher in the MPT group (RR, 5.05; 95%CI, 1.33-19.16; $I^2$, 63%) (Figure 3B)[13,29,34,44].

### MP *versus* BMP

Only one RCT, including 668 patients, assessed BMP compared to MP[18]. Both OS and PFS were longer in the BMP group (OS: HR, 0.61; 95%CI, 0.42-0.89; PFS: HR, 0.48; 95%CI; 0.41-0.56). According to the EBMT (European Group for Blood and Marrow Transplantation) criteria, higher rates for both CR and PR were also attained with BMP (CR: RR, 8.35; 95%CI, 4.68-14.89; $p = 0.0001$; PR: RR, 1.30; 95%CI, 1.06-1.59; $p = 0.01$), while according to the International Uniform Response Criteria (IURC), only CR rate was higher for BMP (RR, 8.39; 95%CI, 4.82-14.60; $p = 0.00001$). The median duration of response was 19.9 months for the BMP group and 13.1 months for the control MP group ($p$ = ns). The median duration of response among patients attaining a CR was 24.0 months in the BMP group and 12.8 months in the MP group (no $p$-value reported). No significant differences were found between the two groups regarding death during treatment (5% and 4% respectively), treatment-related deaths (1% and 2%), overall grade 3-4 toxicities (RR, 1.27; 95%CI, 0.68-2.37) or grade 3-4 hematological toxicity (RR, 1.11; 95%CI, 0.86-1.44). Anemia was significantly reduced in patients treated with BMP (RR, 0.72; 95%CI, 0.56-0.92); however, grade 3-4 peripheral sensory neuropathy (RR, 88.22; 95%CI, 5.45-1426.63) and herpes zoster infections (RR, 3.19; 95% CI, 1.78-5.69) occurred more frequently in the BMP group. An update of the study[43], with a median follow-up of 25.9 months, recently reported a median time to next treatment of 28.1 *versus* 19.2 months (HR, 0.53; $p < 0.000001$), a treatment-free interval of 16.6 *versus* 8.4 months (HR, 0.54; $p < 0.000001$), and a 3-year OS rate of 72% *versus* 59%, for the BMP and MP groups, respectively. The BMP group had a 36% reduced RR of death compared to the MP group (HR, 0.644; $p = 0.0032$). Overall grade 3-4 adverse events and severe adverse events were similar in the two groups (RR, 1.13; 95%CI, 0.94-1.36; $p = 0.19$ and RR, 1.19; 95%CI, 0.83-1.71; $p = 0.35$). Peripheral neuropathy (all grades) was significantly higher in the BMP group (RR, 88.22; 95%CI, 5.15-1477; $p = 0.002$) but improved over time in 79% of cases by a median of 1.9 months; 60% of neurotoxic adverse events were resolved within a median of 5.7 months.

### MP *versus* other chemotherapy regimens without melphalan

Only three studies, including a total of 860 participants, did not include melphalan in the second chemotherapy regimen[29,37,40]. One study compared MP to dexamethasone or dexamethasone plus IFN-α2b[29]; another compared MP to prednisone plus bendamustine[37]; and the third compared MP to VMCP and BCNU[40]. When the three studies were pooled,

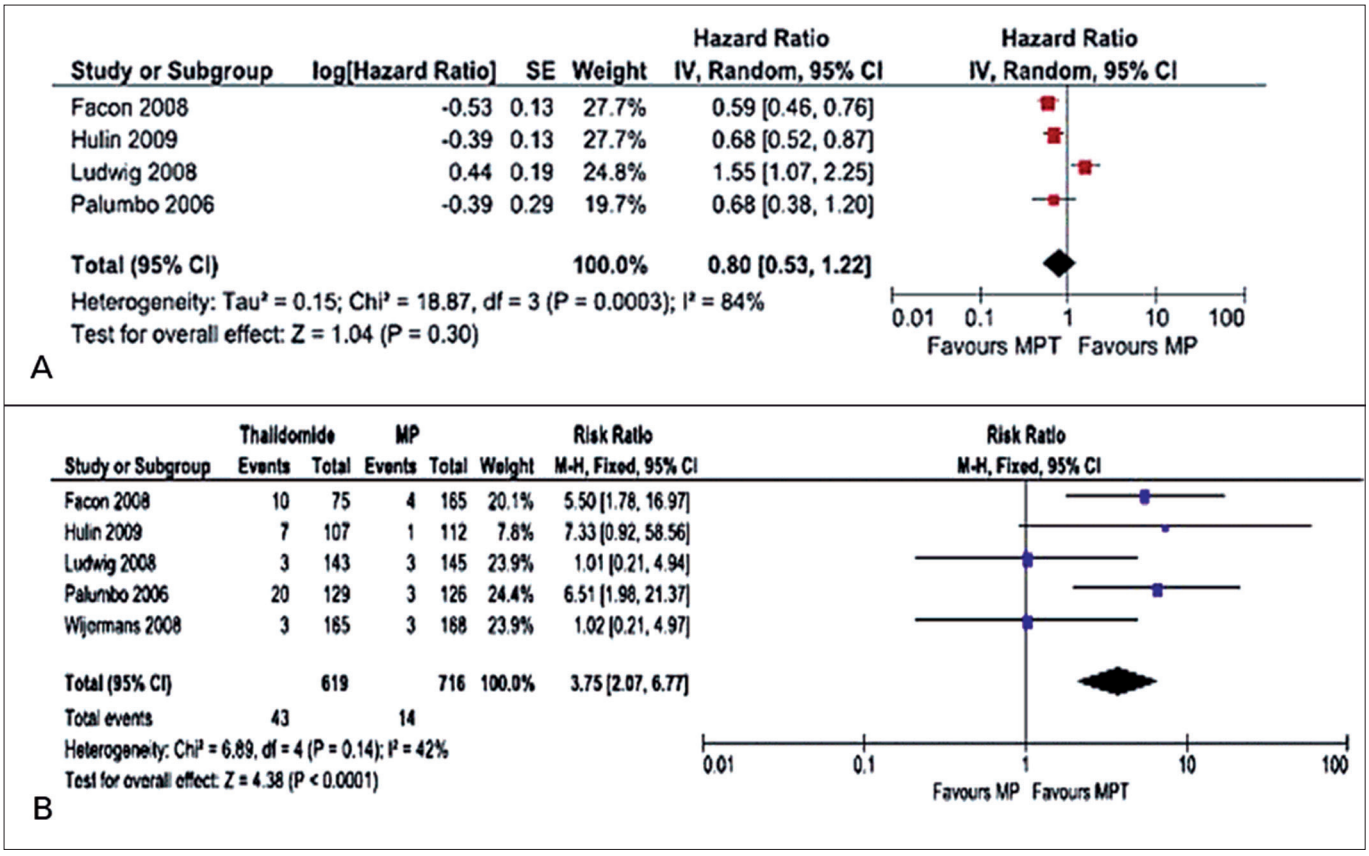


**Figure 2.** A: Meta-analysis of RCT comparing MPT *versus* MP for OS; B: Meta-analysis of RCTs comparing MPT *versus* MP for CR rate.

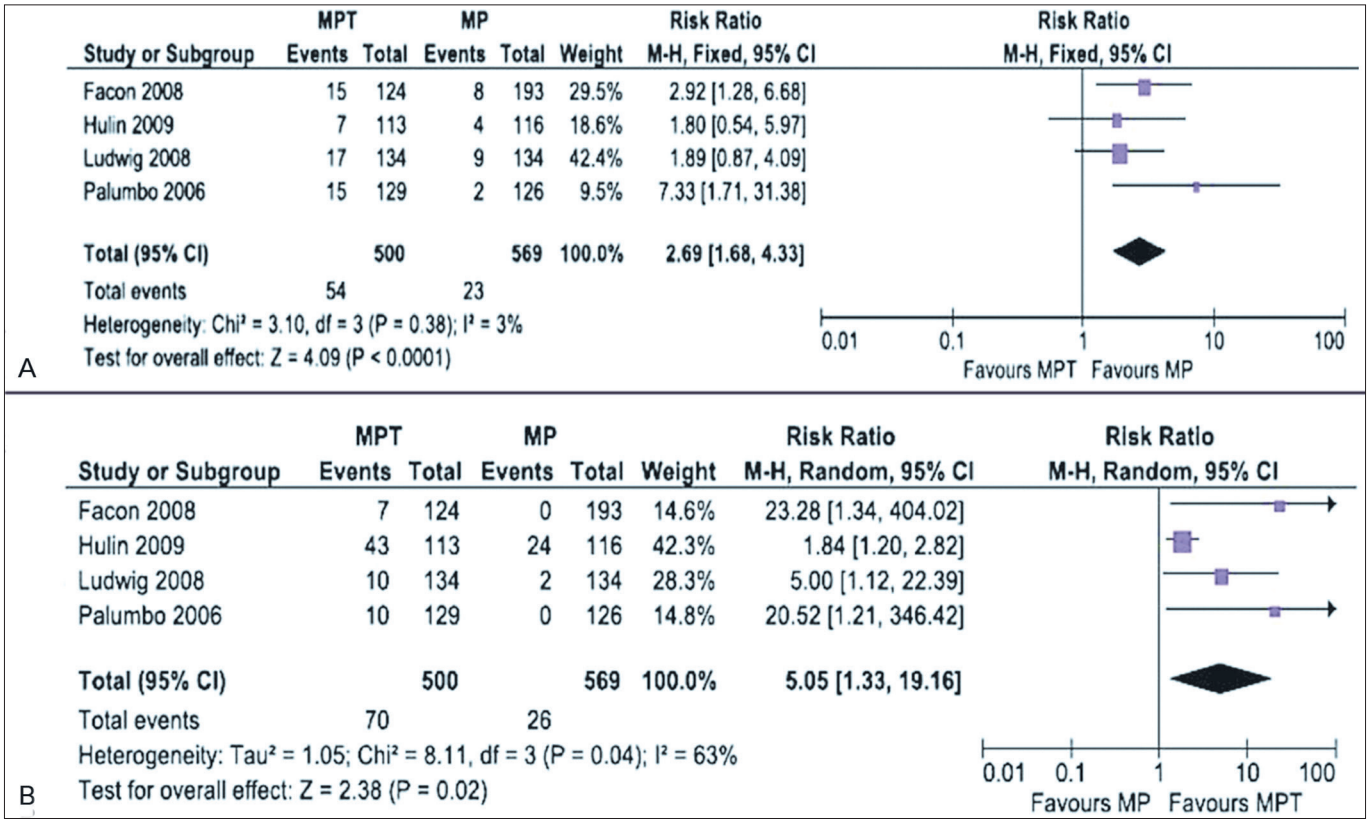


**Figure 3.** A: Meta-analysis of RCTs comparing MPT *versus* MP for thrombosis/embolism; B: Meta-analysis of RCTs comparing MPT *versus* MP for neuropathy.

no significant difference between groups was found in the CR rate (RR, 0.99; 95%CI, 0.10-9.46; $I^2$, 78%). After the first interim analysis, the regimen with dexamethasone was discontinued in the first study[40]. The study comparing prednisone plus bendamustine to MP[37] found no significant difference in OS between the two groups (HR, 1.0; 95%CI, 0.58-1.73). However, a significantly higher number of patients treated with prednisone plus bendamustine achieved a CR compared to those receiving MP (RR, 2.55; 95%CI, 1.22-5.30). Time to disease progression was also longer in patients treated with prednisone plus bendamustine (14 *versus* 10 months; $p < 0.02$). Frequency of anemia, leucopenia and thrombocytopenia were similar in the two groups.

The study comparing MP to dexamethasone-based therapies found no significant differences in OS or in the CR and PR rates at 6 months among the three treatment groups[29]; however, the MP group had less grade 3-4 non-hematological toxicity than dexamethasone alone (RR, 1.70; 95%CI, 1.05-2.76) and dexamethasone plus IFN-α2b (RR, 1.67; 95%CI, 1.02-2.74).

**MP *versus* more aggressive chemotherapy regimens**

Thirteen RCTs, including 3736 patients and 17 different treatment arms, compared more aggressive chemotherapy regimens to MP[23-28,30,32-33,35,36,38,40]. The meta-analysis of all these studies found no significant differences in PR rates between MP and the other chemotherapy regimens (RR, 1.06; 95%CI, 0.49-2.41; $I^2$, 75%). A subgroup analysis of seven RCTs, including a total of 1458 patients, comparing MP to regimens containing vincristine, melphalan, cyclophosphamide and prednisone or vincristine, BCNU, adriamycin and prednisone also found no significant differences in PR rates (RR, 1.14; 95%CI, 0.96-1.36; $I^2$, 53%)[24,25,30,32,35,38,40]. Results of a subgroup analysis of five of the RCTs, with 1395 patients, were similar (RR, 1.09; 95%CI; 0.83-.43; $I^2$, 83%)[23-25,35,38]. In addition, there was no difference in OS, either when all 13 RCTs were pooled or in either of the two subgroup analyses (HR, 0.95; 95%CI, 0.88-1.03; $I^2$, 0%). A significant difference in OS was found in one study comparing MP with reduced-intensity SCT with melphalan (HR, 0.74; 95%CI, 0.56-0.97)[28].

When pooling four RCTs, with 1236 patients, no significant differences were observed in grade 3-4 hematological toxicity (RR, 1.23; 95%CI, 0.85-1.80)[27-28,30,35]. Similarly, when three RCTs, with 1218 patients, were pooled, no differences were observed in grade 3-4 non hematological toxicity (RR, 1.46; 95%CI, 0.90-2.37)[27-28,32]. However, both hematological and non-hematological grade 3-4 toxicities were significantly higher in the group receiving reduced-intensity SCT with melphalan[28].

## DISCUSSION

The gold standard treatment for MM patients is SCT, furthermore, most of elderly ones must receive chemotherapy without SCT[129-141]. We have evaluated the effects of intervention in five chemotherapy groups: MP *versus* MD, MP *versus* MPT, MP *versus* BMP, MP *versus* other chemotherapy regimens without melphalan, and MP *versus* more aggressive chemotherapy regimens.

Our review identified three RCTs[29,31,39] comparing MP to MD. Pooled data showed a significantly higher PR rate in the MD group; however, non-hematological toxicities were also higher with MD, with an increased rate of infections and hyperglycemia, and no differences in OS were observed. Due to higher morbidity rates, these results have led investigators to reject MD as a new standard therapy.

Six studies included thalidomide-based regimens for treating MM patients who were ineligible for SCT[18-19,33,39,46,47], one of which was an update of a previously published study[19]. The thalidomide-based regimens had higher ORR rates in four of these studies[18,33,39,46] and longer PFS in three[18,33,46]. Although OS was also longer in three of the studies[18,33,39], this finding must be interpreted with caution since the studies were quite heterogeneous, due to the wide variety of thalidomide doses (100 to 400 mg/d), the non-universal use of thalidomide as maintenance therapy until disease progression[14,35], and the wide range of chemotherapy cycles used in combination with thalidomide (6 to 12 cycles). Two recent meta-analysis on T-based regimens have found similar benefits in comparison to MP, showing a trend towards better OS[141] and statistically significant increase in OS[142]; however, hampered by remarkable baseline study-to-study heterogeneity, maintenance and relapse therapy. Nevertheless, new combinations avoiding melphalan have been recently evaluated, as in a British RCT that compared first-line chemotherapy with cyclophosphamide, thalidomide, and dexamethasone in 426 patients *versus* melphalan and prednisolone in 423 patients unsuitable for SCT. ORR was significantly higher with the former than with the latter, but the follow-up data could not demonstrate difference in OS[143].

Non-hematological toxicities, mainly thromboembolic defects and peripheral neuropathy, were more frequent in patients receiving thalidomide. A meta-analysis of trials using thalidomide-based therapy described a 9% (95%CI, 6-13%) absolute increase in risk of venous thromboembolic events and a number needed to harm (NNH) of 11 (95%CI, 8-17). Moreover, in six of ten RCTs using thalidomide as induction therapy, no difference was attributable to the non-use of thromboembolic prophylaxis[134]. Only two of the trials[29,126] detected significant improvements in OS. The pooled HR for OS was 0.67 (95%CI, 0.56-0.81) when thalidomide was added to standard non-transplantation therapy, with a negative test for heterogeneity. The weighted RR for response to a thalidomide-containing-regimen was 1.5, which translates to an absolute reduction in the risk of having less than a 24% PR. This suggests that an average of four patients (95%CI, 3-6) need to be treated with thalidomide in order to obtain one additional response. The weighted RR for a CR to induction thalidomide was 2.82[134].

One study compared MP to BMP and found improved ORR, PFS and OS with BMP[18]. This study was closed prematurely based on favorable results[43]. The update confirmed that BMP was associated with a 36% reduction in the risk of death, with median OS not reached in either arm, after a follow up of 25.9 months. Furthermore, BMP showed efficacy regardless of poor prognostic characteristics, including cytogenetic analysis (high-risk defined as t[4;14], t[14;16], del[17p]) by FISH[43]. Importantly, BMP-treated patients were

able to respond to bortezomib-based salvage and immunomodulatory drug-based rescue therapy in similar proportions to patients receiving only MP. This suggests that the initial use of proteasome agent combinations does not necessarily result in significant resistance at a later date[43].

Three studies did not include melphalan in their schedules[29,37,40]; there were no differences in ORR or in OS rates in the group of patients who were treated with dexamethasone or bendamustine without melphalan; nevertheless, there was a higher CR rate and PFS in those receiving bendamustine[37].

Thirteen trials using more aggressive chemotherapy regimens were carried out several decades ago and reported no improvement in any of the outcomes compared to MP. The estimate for proportional reduction in the annual odds of death is 1.5% in favor of combination chemotherapy, but the 95%CI for this reduction ranges from an 8% benefit for chemotherapy to a 5% benefit for MP; this range corresponds to an absolute 1% difference in OS at 3 years[9].

Lenalidomide was not included in our analysis because no RCTs have compared it to MP; however, this novel component seems to offer some advantages over thalidomide, especially in terms of neurotoxicity and ORR[138]. The encouraging data obtained with lenalidomide will provide the basis for new RCTs, such as the current ongoing Eastern Cooperative Oncology Group (ECOG) E4A03 phase III trial, which may lead to its use in patients ineligible for SCT. MP thus continues to be the backbone of treatment for patients not eligible for SCT although newer combinations may improve results and should be considered as part of standard therapy. Our conclusions are supported by the guidelines for the management of MM patients ineligible for standard high-dose chemotherapy with autologous SCT recently published by the International Myeloma Working Group[140].

### Quality of the evidence

Our systematic review and meta-analysis was based on RCTs reported in the literature or presented at major international cancer or hematology conferences. As such, the study has a number of important limitations. Firstly, it is vulnerable to publication bias, nevertheless, the funnel plot decline this observation. We attempted to minimize the potential impact of publication bias by including large and well-designed search strategies, but negative trials or studies conducted in developing countries may have been inadvertently excluded. Since our analysis was limited to published data, in some cases, we had incomplete information. Our integrative review was based on aggregating study and substudy data, not on individual patient information. As a result, our time-to-event analysis was limited and it was not possible to explore whether patient factors contributed to the statistical heterogeneity we observed in some of the outcome analyses. Finally, the quality of a meta-analysis is always subject to the studies included in the review. All our included studies were opened and only four RCTs had a low risk of bias; the other 18 trials were judged to have an unclear risk of bias, mainly because the description of the method used for generating the allocation sequence and/or concealing the allocation was unclear. The absence of blinding had minimal relevance for the analysis of outcomes such as OS or PFS but may have affected adverse event rates. Furthermore, most RCTs did not calculate sample size, which represents a potential source of imprecision, and some of the studies reported preliminary results for which it was impossible to obtain predefined statistical parameters[18].

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**Annex 1.** Characteristics of RCTs included in the review.

| Study | Methods | Participants | Interventions | Outcomes |
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| Blade 1990 | Multicenter RCT, open label study with parallel design, unblinded. N = 386 | Naïve patients with MM diagnosis according to the Chronic Leukemia Myeloma Task Force (1973). Patients with asymptomatic disease were excluded. | a. MP[1] alterning with b. VCMP[1]/VBAP[1] (courses were administered at 4-week intervals) | Evaluation of response was made after eight cycles of chemotherapy. Response was defined as a reduction of 50% or more of the monoclonal component, improvement in PS by at least two grades, and a decrease greater than 50% in measured cross-sectional area of plasmacytomas. Furthermore, the size and number of lytic bone lesions must not have increased, and there also must have been correction of hypercalcemia (< 11.5 mg/dL), anemia (> 9 g/dL), and hypoalbuminemia (> 3 g/dL). Those patients who fulfilled all of the above criteria but who had a less than 50% reduction of M-component were considered to have had a partial response. When the criteria for objective or partial response were not accomplished, the case was considered as a treatment failure. Relapse was defined as an increase greater than 50% from the lowest level of serum M-component achieved with the initial therapy, an increase in size or number of lytic bone lesions, and development of extraosseous plasmacytomas, anemia, or hypercalcemia. |

**Continued Annex 1.**

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| Blade 1993 | Multicenter RCT, open label, unblinded. N= 449 (248 and 239 patients were randomized to receive MP[1] and alternating courses of VCMP[1]/VBAP[1], respectively). | Naïve patients with MM diagnosis according to the Chronic Leukemia Myeloma Task Force (1973). Patients with asymptomatic disease were excluded. | MP[1] alterning with VCMP[1]/VBAP[1] (courses administered at 4-week intervals and patients with serum creatinine > 2 mg/dL initially received the alkylating agents at half doses) | Evaluation of response was made after eight cycles of chemotherapy. Response was defined as a reduction of 50% or more of the monoclonal component, improvement in PS by at least two grades, and a decrease greater than 50% in measured cross-sectional area of plasmacytomas. Furthermore, the size and number of lytic bone lesions must not have increased, and there also must have been correction of hypercalcemia (< 11.5 mg/dL), anemia (> 9 g/dL), and hypoalbuminemia (> 3 g/dL). Those patients who fulfilled all of the above criteria but who had a less than 50% reduction of M-component were considered to have had a partial response. When the criteria for objective or partial response were not accomplished, the case was considered as a treatment failure. Relapse was defined as an increase greater than 50% from the lowest level of serum M-component achieved with the initial therapy, an increase in size or number of lytic bone lesions, and development of extraosseous plasmacytomas, anemia, or hypercalcemia. |
| Boccadoro 1991 | Multicenter RCT, open label. N = 304 | Naïve patients with MM according to the SWOG criteria. MM was classified using the Durie and Salmon staging system. | MP[2] VMCP[2]/VBAP[2] (induction treatment was administered at 28-day intervals for 12 months) | Response was defined as a reduction of 50% or more in the M-component. Relapse was defined as an increase greater than 100% from the lowest level of serum M--component, or a raise in the size or number of lytic bone lesions. Progression were defined for never-responding population as an increase greater than 25% in the M--component or an increase in size or number of lytic bone lesions during induction treatment. |
| Cavo 2002 | Multicenter RCT, open label, unblinded. N = 542 (patients were assigned in blocks of six to receive one of three regimens consisting of either MP[3] alone, VAD alternating with MP[3] or VND alternating with MP[3]). Randomization to the three arms of the study was 1:1:1. Patients were planned to receive 8-monthly courses of chemotherapy. Of the 527 eligible patients, 179 were randomly assigned to MP[3], 174 to arm alternating VAD/MP[3], and 174 to alternating VND/MP[3]. | Naïve patients with MM diagnosis according to the Chronic Leukemia Myeloma Task Force (1973) Patients were eligible for randomization if they had symptomatic MM and measurable M-protein in the serum and/or urine. Reasons for exclusion included age > 80 years, severe heart disease, hepatic dysfunction or prior history of another neoplasm. Patients with smoldering myeloma, localized plasmacytoma or plasma cell leukemia were also excluded. | MP[3] VAD VND Full drug doses were administered if granulocytes > $2\times10^9$/L and platelets > $100\times10^9$/L. Patients who completed the induction chemotherapy phase of the study and achieved an objective response received recombinant interferon (IFN) α-2b at the dose of 3 MU, subcutaneously, three times weekly, until evidence of progression. | Response was evaluated according to the criteria of the Chronic-Leukemia Myeloma Task Force and was based on M-protein decrease at the end of induction chemotherapy as compared with pre- treatment values. An objective response was defined by a decrease in serum or urinary M-protein concentration of at least 50% or 75%, respectively, without other evidence of progression. Patients who achieved only a 25% to 50% decrease in serum M-protein level or at least 50% reduction in 24-hour excretion of urinary light chains were considered as having a minor response. Stable disease, or no change, included less than 25% decrease in serum M protein level or less than 50% reduction in Bence Jones proteinuria. Progression was defined as a confirmed increase in M--protein concentration of more than 25% above pretreatment values and/or an increase in size or number of lytic bone lesions either during or after completion of induction chemotherapy. |
| Cooper 1986 | Multicenter RCT, with parallel design and open label. N = 615 (patients were randomized to receive MCBP, sequentially-MCBP, MCBPA or MP[4]) | The diagnosis of MM was established according to the criteria of the Chronic Leukemia-Myeloma Task Force. Any patient had received prior chemotherapy and prior radiation treatment of symptomatic lesions was allowed if the field did not exceed 150 $cm^2$ and if the course of treatment was completed before protocol entry. | MCBP (repeated every 42 days) Seq-MCBP (repeated every 84 days) MCBPA (repeated every 42 days) MP[4] (repeated every 28 days) | Complete response was defined as a reduction of serum or urinary M-protein to 50% of the initial value, healing of bone lesions, or 50% decrease in the area of measured soft-tissue lesions. Indirect responses included improvement in hemoglobin level, creatinine, serum calcium, PS, or pain. |

**Continued Annex 1.**

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| Facon 2005 | RCT, multicenter, parallel, open label. N = 104. (Patients were randomized to receive MP[5], M-DEX[1], DEX[1], or DEX-IFN in a 1:1:1:1 ratio.) Following the interim analysis, the data safety monitoring board (DSMB) recommended stopping enrollment in the DEX[1] arm based on a striking disadvantage in terms of progression-free survival ($p$ = .001) of DEX[1] as compared with M groups (MP[5] and M-DEX[1]) and a trend on OS ($p$ =.03). | Patients aged between 65 and 75 years and fulfilling a diagnosis of stage II or III MM according to the Durie and Salmon criteria, or stage I MM patients if they met one of the criteria defining high--risk stage I. Patients were previously untreated (except the minimum dose of radiotherapy to localized lesions required to relieve symptoms). Patients were excluded if they: met the criteria of primary amyloidosis; had a prior history of another neoplasm or of seizure; had significant cardiac, psychiatric or hepatic dysfunction; had a contraindication to high-dose steroids. | a. MP[5]: Courses were administered at 6-week intervals for 12 cycles. The neutrophil count must have reached 1.5x10$^9$/L and the platelet count 100x10$^9$/L before full-dose chemotherapy was given. A 50% melphalan reduction was performed if the neutrophil count was between 1.0x10$^9$/L and 1.5x10$^9$/L or the platelet count between 50x10$^9$/L and 100x10$^9$/L. b. DEX[1]: On 12 cycles. The dose could be reduced by 50% (20 mg/d) in case of toxicity c. M-DEX[1]: The doses of melphalan and dexamethasone and dose adjustments for side effects were the same as those presented for the MP[5] and dexamethasone regimens. d. DEX-IFN: IFN was permanently discontinued in the case of an emergence of cardiac dysfunction or an occurrence of seizures or psychiatric complications. Protocol doses of IFN were reduced by 20% to 50% in patients who experienced significant fatigue or other symptoms suggesting significant toxicity. The dose was subsequently reescalated if this was feasible. | Overall survival, progression-free survival, survival after progression, response rates, and toxicities. Any response required an improvement in bone pain and performance status, correction of hypercalcaemia, and no increase in size or number of lytic bone lesions. Partial response: reduction in the size of soft-tissue plasmacytomas, 50% reduction in serum monoclonal protein and 24-hour urinary light chain excretion by 75% or more. Complete response: absence of the original monoclonal protein in serum and urine by immunofixation, less than 5% plasma cells in a bone marrow aspirate, disappearance of soft tissue plasmacytomas. Progressive disease: more than 25% increase in serum monoclonal protein, 50% increase in the 24-hour urinary light chain excretion, increase in the size or new of bone lesions or soft-tissue plasmocytomas, hypercalcaemia not attributable to any other cause. Stable disease: Patients not meeting the criteria of either partial or complete response or progressive disease. |
| Facon 2006 | RCT, multicenter, open label. N = 447 (patients were randomly assigned, 126 assigned to MP[5], 125 to MP[5] plus thalidomide and 126 to MEL100.) | Untreated patients aged between 65 and 75 years and fulfilling a diagnosis of stage II or III MM according to the Durie and Salmon criteria, or stage I MM patients if they met one of the criteria defining high-risk stage I patients. If younger, were included if they were ineligible for high-dose treatment. Exclusion criteria: previous history of another neoplasm (except basocellular cutaneous or cervical epithelioma); primary or associated amyloidosis; a WHO performance index of 3 or greater, if unrelated to MM; substantial renal insufficiency with creatinine serum concentration of 50 mg/L or more; cardiac or hepatic dysfunction; peripheral neuropathy; or infection with HIV, or hepatitis B or C. | a. MP[5] every 6 weeks, 12 cycles. b. MP[5] every 6 weeks, 12 cycles plus Thalidomide given daily at a dose not exceeding 400 mg per day, continuously during the 12 MP[5] cycles. Thalidomide was stopped at day 4 of the last melphalan and prednisone cycle. c. Stem-cell support (MEL100): All patients receiving MEL100 had two debulking courses of VAD[1] 4 weeks apart: Peripheral blood stem cells were mobilised by administration of 3 g/m$^2$ of cyclophosphamide with subsequent mesna (sodium 2-mercaptoethane ulfonate). Granulocyte colony-Stimulating factor (G-CSF, Granocyte,) was given at 10 µg/kg on day 1 through the last day of leukapheresis initiated upon recovery of leucocytes to 4x10$^9$/L. The minimum number of obtained CD34 cells neded was 2x10$^6$/kg per melphalan 100 mg/m$^2$ course. The first course was followed by the reinfusion of stem cells 36 h later. G-CSF was given at 150 µg/m$^2$ on day 5 until neutrophil recovery. The second course of melphan 100 mg/m2 was repeated after 2 months. | Overall survival, response, progression-free survival, survival after progression and toxicity. Complete response: absence of the original monoclonal protein in serum and urine, less than 5% of plasma cells in a bone-marrow aspirate, and the disappearance of soft--tissue plasmacytomas Progressive disease: 25% increase in the concentration of serum monoclonal protein, 50% increase in the 24-h urinary light chain excretion, increase in the size or new bone lesions or soft-tissue plasmacytomas, hypercalcaemia, not attributable to any cause other than MM. Best response at 12 months: the highest amount of disease improvement achieved by a patient, except if progressive disease had occurred during that period without response assessment at 12 months (between 9 and 15 months). |
| Hansen 1985 | RCT N = 104 MP[6] = 33 MVP[1] = 32 VBCMP[1] = 31 | All previously untreated patients with a confirmed diagnosis of MM were eligible. Diagnostic criteria for MM: a) more than 3% atypical plasma cells in a bone marrow smear combined with b) at least 1 of the following 3 criteria: (i) an M-component in serum in a high concentration or (ii) excretion of light chains in the urine > 0.25 g/24 h, or (iii) osteolytic bone lesions. | a. MP[6] b. MVP[1] c. VBCMP[1] | Response: a decrease in M component concentration in serum or urine of 75% or more; the osteolytic lesions must not have enlarged > 25% or increased in number, the serum calcium concentration must have remained normal and a decrease of 25% or a normalization of an increased serum Creatinine and a 25% increase or a normalization of HB. |

**Continued Annex 1.**

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| Hernandez 2004 | RCT, multicenter, open label. Only 170 (87 MP[1] and 83 DEX[2]) patients were evaluable for response. | Diagnostic criteria of the Chronic Leukemia Myeloma Task Force of the National Cancer Institute (1973) and be diagnosed with symptomatic MM. | a. MP[1]<br>b. DEX[2] | Response rate, event-free survival, overall survival and toxicity. Those patients who showed disappearance of the M-Component by electrophoresis and < 5% plasma cells in bone marrow were considered complete responders. |
| HJORT 1990 | RCT, multicenter. N = 164MP[5] = 85 Multidrug chemotherapy (MDC) = 79 | Inclusion criteria: (A) serum M-protein concentration above 30 g/L (IgG) or 20 g/L (IgA) and/or Bence Jones proteinuria > 1 g/24h. B) Bone marrow plasma cells > 10% and (C) Osteolitic bone lesions. A diagnosis of MM was accepted if criteria A+B or A+C were fulfilled. | a. MP[5] every 6 weeks.<br>b. For patients randomized to MDC:<br>(i) stage II patients were given VMCP[3] every 4 weeks,<br>(ii) stage III patients were given VBAP[3] and VMCP[3] alternately every 4 weeks. | Response remission: 50% reduction of the initial M-protein concentration.<br>Time to response: from the start of treatment until the first confirmed M-protein determination showing at least a 50% reduction.<br>Relapse: increase in M protein of > 20% or the reappearance of a vanished M-protein. |
| Kildahl-Andersen 1988 | RCT, multicenter. N = 92 VCCM[1] = 48 MP[7] = 44 | 92 Patients with MM diagnosed according to the criteria recommended by the Chronic Leukemia-Myeloma Task Force and the South West Oncology Group. No patient received prior chemotherapy. Staging performed according to Durie & Salmon. | a. VCCM[1]<br>b. MP[7] | Median Survival, time to relapse, duration of remission, Response rate.<br>The criteria for response were those adopted by the Chronic Leukemia-Myeloma Task Force 1973. |
| Ludwig 2008 | Multicenter, open label. N = 289 TD[1] = 145 MP[5] = 144 19 and 15 withdrawals respectively occurred during follow up. | Previously untreated active MM not eligible for autologous transplantation with Durie Salmon stage II and III, and stage I on high risk. Exclusion criteria: Extramedullary or solitary plasmacytoma without evidence of dissemination of disease or with smouldering myeloma, with more than 3 irradiation fields, congestive heart failure (NYHA III and IV), acute infection, uncontrolled medical condition. | a. TD[1]: standard doses on odd cycles and same dose added on day 15 - 18 on even cycles of 28 days.<br>b. MP[5]: during a 28 to 42 day cycle. | Progression-free survival, tolerance, response rates, time to response, overall survival.<br>Evaluation of response, the EBMT criteria: Disappearance of myeloma protein in serum and urine by immunofixation maintained for a minimum of 6 weeks, < 5% plasma cells in bone marrow, no increase in lytic bone lesions, disappearance of soft tissue plasmacytomas.<br>Progression of the disease: A greater than 25% increase in serum paraprotein concentrationa and in 24-hour urinary paraprotein excretion, > 25% increase in plasma cells, progressive bone disease, hypercalcaemia not attributable to other causes than myeloma. |
| Osterborg 1989 | RCT, multicenter. N = 86 MP[5] = 44 VCMP[4]/VBAP[4] = 42 | Patients with MM stage III. Diagnosis: When at least two of following criteria was met: 1. A monoclonal immunoglobulin peak with a subnormal concentration of at least one non-monoclonal immunoglobulin class (IgG, IgM and IgA) 2. > 10% plasma cells in the bone marrow. 3. Osteolytic and or osteoporotic bone lesions compatible with MM. | a. VCMP[4] alternating every 3 weeks with VBAP[4]. When response was achieved, interval between the cycles was prolonged to 6 weeks.<br>b. MP[5] administered at 6-week intervals, continued until progression or relapse. | The criteria for response were those adopted by the Chronic Leukemia-Myeloma Task Force 1973. |
| Palumbo 2006 | RCT, multicenter. MPT[1] = 129 MP[8] = 126 There were 10 withdrawals (7 lost to follow up in MP[8]) | Inclusion criteria: previously untreated MM patients older than 65 years (or younger but unable to undergo transplantation), Durie and Salmon stage II or III myeloma, and measurable disease. Exclusion criteria: another cancer, psychiatric disease and any grade 2 peripheral neuropathy. | a. MP[8]: every 4 weeks for six cycles. In this group, patients who had progressive disease or relapse were permitted to crossover to receive thalidomide as salvage treatment.<br>b. MPT[1] every 4 weeks for six cycles. | Clinical response rates, event-free survival, overall survival, prognostic factors, time to the first evidence of response, incidence of any grade 3 or higher adverse events.<br>Response criteria of the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry were used. |

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| Palumbo 2008 | RCT, multicenter.<br>N = 331<br>MPT[1] = 167<br>MP[8] = 164 | Patients with previously untreated MM who were older than 65 years or younger not candidates for transplant, Durie and Salmon stage II or III MM, with measurable disease. | a. MPT[1]: every 6 weeks for six cycles. The dose of Thalidomide was reduced by 50% on the occurrence of any non-hematologic grade 2 toxicity and was discontinued for any non-hematologic grade 3 toxicity.<br>Enoxaparin 40 mg day was given subcutaneously during the first 4 cycles of therapy, as anticoagulation prophylaxis.<br>b. MP[8]: every 6 weeks. | Response rates, progression-free survival, overall survival, prognostic factors and adverse events.<br>Response to treament: Criteria of European Group for Blood and Marrow Transplantation-Intenational Bone Marrow Transplant Registry. |
| Pavlovsky 1984 | RCT<br>N = 234 previously untreated<br>patients MP[9] = 129<br>MPCVM[1] = 105 | 239 untreated patients with MM | a. MP[9]b. MPCVM[1] | Good response: reduction of > 50% in serum M-protein concentration or > 75% in urinary M-protein excretion and a decrease of > 50% in measured cross-sectional area of a plasmacytoma.<br>Partial response: decrease of < 50% in serum and/or < 75% in urinary M-protein with an increase in haemoglobin in the absence of blood transfusion and performance status. |
| Pönisch 2006 | RCT<br>BP[1] = 68<br>MP[10] = 63<br>Randomization was stratified by the stage of the disease. | Inclusion criteria: Durie and Salmon criteria for stage II with progression or stage III MM, quantitatively measurable myeloma proteins in the serum and/or urine, leukocyte count > 2,000/L, platelet count > 50,000/L, Karnofsky performance status of 60%, life expectancy of > 3 months, no prior chemotherapy or radiotherapy.<br>Exclusion criteria: Patients with nonsecretory and local plasmacytoma, HIV or Hbs-AG positivity or active hepatitis, secondary malignancy, pregnancy, lactation or inadequate contraception. | a. MP[10]<br>b. BP[1]<br>Treatment with MP[10] or BP[1] was administered every 28 days until maximum remission or disease progression was observed. | Complete remission: decline in serum myeloma protein by > 75% to < 25 g/l, reduction in 24-h urinary protein by > 90% to < 200 mg/24 h, no increase in skeletal destruction, serum calcium within normal range, no blood transfusion required in the previous 3 months.<br>Partial remission: decline 25%-74% in serum myeloma protein, reduction in 24-h urinary myeloma protein of 25%-89%, no increase in skeletal destruction, and serum calcium within normal range.<br>No change: only minor variations (< ± 25%) in serum myeloma protein and/or 24-h urinary protein.<br>Progressive disease: increase in serum and/or 24-h urinary protein by at least 25%, new osteolytic lesions, hypercalcemia, worsening of anemia with increased infiltration of plasma cells into the bone marrow. |
| Salmon 1983 | RCT<br>N = 237<br>a. VCMP[5] and VCAP[1] = 160<br>b. MP[11] = 77 | Previously untreated patients with MM. The diagnosis was established according to criteria by the Chronic Leukemia-Myeloma Task Force and the SWOG. | Three arms:<br>a. Alternating combination of VCMP[5] and VCAP[1]<br>b. A syncopated alternation of three cycles of VCMP[5] followed by three cycles of VBAP[5]<br>c. MP[11]<br>Of those patients evaluable for response to induction therapy, 160 were randomized to alternating combination therapy (80 to VCMP[5] + VCAP[1] and 80 to VCMP[5] + VBAP[5]) and 77 to MP[11]. Patients who had achieved remission were then randomized to maintenance treatment with VCMP[5] alone or in combination with Levamisole 100 mg/m$^2$ PO on days 6 and 7, and days 13 and 14 of each cycle of VCMP[5] chemotherapy. | SWOG criteria objective remission status: At least a 75% reduction in the rate of M-component production and tumor burdens, and improvement in other response criteria (e.g., anemia and hypercalcaemia). |
| San Miguel 2008 | RCT, multicenter, open label.<br>N = 682<br>MP[1] plus Bortezomib = 344<br>MP[1] = 338<br>Randomization was stratified according to baseline levels of β2- microglobulin. | Patients with newly diagnosed, untreated, symptomatic, measurable MM who were not candidates for stem-cell transplantation because of age (≥ 65 years) or coexisting conditions were eligible. | a. MP[1] every 6 weeks.<br>b. MP[1] every 6 weeks plus Bortezomib 1.3 mg/m$^2$, by intravenous bolus on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9. | Time to disease progression, rate of complete response, duration of response, time to subsequent myeloma therapy, overall survival.<br>Using criteria of the European Group for Blood and Marrow Transplantation (EBMT). The rate of serious adverse events in the bortezomib group was higher than that in the control group (46% *vs.* 36%). |

**Continued Annex 1.**

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| Shustik, 2006 | RCT.<br>N = 466<br>DEX[3] = 232<br>MP[12] = 234<br>Assessment or maintenance with Desamethasone = 292<br>Observation = 147<br>Dexamethasone = 145 | Patients with previously untreated, symptomatic stage I or stages II-III MM using the Salmon-Durie classification. Patients with previously untreated, symptomatic stage I or stages II-III MM using the Salmon-Durie classification. Inclusion criteria: Histological confirmation of MM and a measurable serum monoclonal paraprotein or urinary excretion of at least 1.0 g of monoclonal light chain protein in 24 h. Patients with marrow plasmacytosis at < 10% were eligible if a measurable serum or urine paraprotein was present with at least one osteolytic bone lesion.<br>Exclusion criteria: Comorbid condition, cancer other than adequately treated squamous or basal cell carcinoma of the skin, carcinoma *in situ* of the cervix, or cancer that was treated more than 5 years before study, peptic ulcer disease. | Four treatment arms: Induction treatment with MP[12] or DEX[3] and maintenance management with observation or dexamethasone.<br>MP[12] was given every 28 days. If after two treatment cycles, a stable or rising monoclonal protein was observed and nadir neutropenia of < 0.5 x $10^9$/L was not observed, doses were escalated by 3 mg/$m^2$ with subsequent cycles.<br>DEX[3] was given every 14 days for the first 84 days (3 treatment cycles) and then every 28 days with remaining cycles.<br>Patients were to receive twelve 28-day cycles of therapy: doses were attenuated or deleted according to treatment-related toxicities.<br>Patients who did not demonstrate disease progression after completing induction therapy were, as per their initial allocation, either observed or received dexamethasone 40 mg per day for 4 days every 28 days until experiencing dose--limiting toxicity or progressive myeloma.<br>Patients with a satisfactory response to treatment, and who, subsequently experienced progressive myeloma, were retreated with their assigned induction treatment; if the initial response to therapy was unsatisfactory, patients received subsequent therapy off study. | Overall survival, response to treatment, progression- free survival, treatment-related toxicity.<br>Criteria for response: Reduction in the serum monoclonal paraprotein by at least 50% and a reduction in the 24-h urine excretion of monoclonal light chain by at least 90%.<br>Criteria for progressive disease: Increase in the serum monoclonal paraprotein to least 50% above the baseline value and in the 24-h urinary monoclonal light chain excretion to > 100% above baseline, hipercalcemia despite chemotherapy, new lytic bone lesion, progressive cytopenia in conjunction with increasing marrow plasmacytosis. |
| Tribalto 1985 | RCT.<br>N = 133 previously untreated patient.<br>N = 133<br>MP[13] = 47<br>VCMP[6] = 53<br>PCB[1] = 33 | Only previously untreated patients with diagnosis of MM according to the South Western Oncology Group (SWOG) criteria. Patients were stratified according to Durie & Salmon System. The presence or absence of normal renal function (BUN < 40 mg%, creatinine < 2 mg%) subclassified patients into A and B groups. | a. MP[13], monthly x 6.b. VCMP[6], monthly x 6.c. PCB[1], 3 Cycles monthly. | Criteria for response by the South Western Oncology Group (SWOG) criteria: Decrease in the M-proteins of 75% or more, and to less than 2.5 g/dL, a > 90% decrease in 24-h urine globulin, not increment in size and number of lytic skull lesions, serum calcium remained normal, correction of anemia and hypoalbuminemia.<br>Patients with 50-75% decrease in M-protein were considered to be improved. If not satisfy any of these categories, were deemed unresponsive.<br>Progression: Increase in M-protein of at least 1.0 g/dL, a 100% increase in the protein excreted in the urine per 24h, hypercalcaemia > 11.0 mg/dl, plasmacytomas that enlarge progressively<br>Relapse: Rise in M-protein over 50% of the pre-study level, rise in calcium > 11.0 mg/dL, development of plasmacytoma |
| Wijermans 2008 | RCT<br>N=301<br>a. MP[14] = 149<br>b. MP[14] plus Thalidomide = 152 | Patients with previous untreated MM > 65 years of age with a stage IB or higher. | a. MP[14] every 4 weeks.<br>b. MP[14] every 4 weeks plus Thalidomide 200 mg daily.<br>A maximum of 8 cycles was planned. In case of ongoing improvement of response, further therapy was allowed until a plateau phase was reached. When a good response and a plateau phase was reached, the patients on MP[14] plus Thalidomide received maintenance therapy with Thalidomide 50 mg/day until disease progression. | Event Free Survival, Progression Free Survival, Overall Survival, Response Rate.<br>Responses were assessed using the IMWG criteria. |

**Continued Annex 1.**

| | | | | |
|---|---|---|---|---|
| Hulin 2009 | RCT, Multicenter, placebo study.<br>N = 229<br>a. MP[15] plus Placebo = 116<br>b. MP[15] plus Thalidomide = 113 | Patients had stage II or III, newly diagnosed MM, according to Durie-Salmon criteria and were at least 75 years of age. Durie-Salmon stage I MM could be enrolled if they met the criteria of high-risk stage I disease.<br>Exclusion criteria: previous neoplasms, amyloidosis, a WHO performance index of 3 or higher, renal insufficiency with creatinine serum concentration of 50 mg/L or more; cardiac or hepatic dysfunction; peripheral neuropathy; history of venous thrombosis during the previous 6 months; HIV infection, or hepatitis B or C infections. | a. MP[15] plus Placebo;<br>b. MP[15] plus Thalidomide 100mg Placebo or thalidomide was given continuously for 72 weeks, administered at bedtime. A dose reduction to 50 mg per day of Thalidomide or placebo was allowed at the investigator discretion in the event of patient intolerance, especially in case of mild or moderate peripheral neuropathy (grade 1 or 2). | Overall survival, safety, response rates, and progression--free survival. |

RCT: randomized controlled trial; MM: MM; PS: performance status.
MP[1]: melphalan 9 mg/m$^2$ PO days 1-4 + prednisone 60 mg/m$^2$ day PO or IM days 1-4.MP[2]: melphalan 6 mg/m$^2$ PO days 1-7 + prednisone 60 mg/m$^2$ PO days 1-7.
MP[3]: melphalan 10 mg/m$^2$ PO days 1-4 + prednisone 80 mg/m$^2$ IM days 1-4.
MP[4]: melphalan 16 mg/m$^2$ PO days 1, 15, 29, 43, and every 28 days thereafter + 6-week tapering course of prednisone beginning at a dose of 0.8 mg/kg for 14 days, with reductions to 0.4 mg/kg days 15-28, and 0.2 mg/kg days 29-42.
MP[5]: melphalan 0.25 mg/kg PO days 1-4 + prednisone 2 mg/kg PO days 1-4.
MP[6]: melphalan 0.15 mg/kg PO days 1-7 every 4 weeks + prednisone.
MP[7]: melphalan 0.25 mg/kg PO days 1-4 + prednisone 100-150 mg dependent of weight PO days 1-4.
MP[8]: melphalan 4 mg/m$^2$ PO days 1-7 + prednisone 40 mg/m$^2$ PO days 1-7.
MP[9]: melphalan 8 mg/m$^2$ PO days 1-4 + prednisone 40 mg/m$^2$ PO days 1-7 every 4 weeks.
MP[10]: melphalan 15 mg/m$^2$ in 500ml NaCl 0.9% infusion over 30 minutes day 1 + prednisone 60 mg/m$^2$ PO or IV days 1-4.
MP[11]: melphalan 8 mg/m$^2$ PO days 1-4 + prednisone 60 mg/m$^2$ days 1-4.
MP[12]: melphalan 9 mg/m$^2$ PO days 1-4 + prednisone 100 mg/m$^2$ PO days 1-4.
MP[13]: melphalan 0.1 mg/kg PO days 1-7 + prednisone 40 mg/m$^2$.
MP[14]: melphalan 0.25 mg/kg PO days 1-5 + prednisone 1 mg/kg PO days 1-5.
MP[15]: melphalan 0.2 mg/kg PO days 1-4 + prednisone 2 mg/kg days 1-4 every 6 weeks, by 12 cycles.
MPT[1]: melphalan 4 mg/m$^2$ PO days 1-7 + prednisone 40 mg/m$^2$ PO days 1-7 + thalidomide 100 mg PO continuously at all cycle and as maintenance therapy until evidence of relapse or refractory disease.
MVP[1]: melphalan 0.15 mg/kg PO day 1 + vincristine 0.03 mg/kg (max 2 mg) IV day 1; every week + prednisone.
MPCVM[1]: melphalan 8 mg/m$^2$ PO days 1-4 + prednisone 40 mg/m$^2$ PO days 1-7 every 4 weeks + Cyclophosphamide 600 mg/m$^2$ IV day 1 + Vincristine 0.6 mg/m$^2$ IV day 1 every 4 weeks and MeCCNU 100 mg/m$^2$ PO day 1 every 8 weeks.
BP[1]: Bendamustine 150 mg/m$^2$ in 500 ml NaCl 0.9% infusion over 30 minutes days 1-2 + prednisone 60 mg/m$^2$ IV or PO days 1-4.
VCMP[1]: vincristine 1 mg IV day 1 + cyclophosphamide 500 mg/m$^2$ IV day 1 + melphalan 6 mg/m$^2$ PO days 1-4 + prednisone 60 mg/m$^2$ IV or IM days 1-4.
VCMP[2]: vincristine 1 mg IV day 1 + cyclophosphamide 120 mg/m$^2$ PO days 1-7 + melphalan 6 mg/m$^2$ PO days 1-7 + prednisone 60 mg/m$^2$ PO days 1-7.
VCMP[3]: vincristine 1 mg IV day 1 + cyclophosphamide 100 mg/m$^2$ IV day 14 + melphalan 5 mg/m$^2$ PO day 1 + prednisone 60 mg/m$^2$ IV day 14.
VCMP[4]: vincristine 1 mg IV day 1 + cyclophosphamide 100 mg/m$^2$ PO days 1-4 + melphalan 5 mg/m$^2$ PO days 1-4 + prednisone 60 mg/m$^2$ PO days 1-3.
VCMP[5]: vincristine 1 mg/m$^2$ (maximum 1.5 mg) IV + cyclophosphamide 125 mg/m$^2$ PO days 1-4 + melphalan 6 mg/m$^2$ PO days 1-4 + prednisone 60 mg/m$^2$ PO days 1-4.
VCMP[6]: vincristine 1 mg IV day 1 + ciclosphamide 125 mg/m$^2$ days 1-7 + melphalan 6 mg/m$^2$ days 1-7 + prednisone 60 mg/m$^2$ PO days 1-7.
VBCMP[1]: melphalan 0.1 mg/kg PO days 1-7 + BCNU 0.5 mg/kg IV day 1 + cyclophosphamide 10 mg/kg IV day 1 + vincristine 0.03 mg/kg (max 2 mg) IV day 1; every 5 weeks + prednisone
VBAP[1]: vincristine 1 mg IV day 1 + carmustine 30 mg/m$^2$ IV day 1 + doxorubicin 30 mg/m$^2$ IV day 1 + prednisone 60 mg/m$^2$ IV or IM days 1-4.
VBAP[2]: vincristine 1 mg IV day 1 + carmustine 30 mg/m$^2$ IV day 1 + doxorubicin 30 mg/m$^2$ IV day 1 + prednisone 60 mg/m$^2$ PO days 1-7.
VBAP[3]: vincristine 1 mg IV day 1 + carmustine 30 mg/m$^2$ IV day 1 + doxorubicin 30 mg/m$^2$ IV day 1 + prednisone 60 mg/m$^2$ PO days 1-4.
VBAP[4]: vincristine 1 mg IV day 1 + BCNU 30 mg/m$^2$ IV day 1 + adriamycin 25 mg/m$^2$ IV day 1 + prednisone 60 mg/m$^2$ PO days 1-4.
VBAP[5]: vincristine 1 mg/m$^2$ (maximum 1.5 mg) IV + carmustine 30 mg/m$^2$ IV day 1 + doxorubicin 30 mg/m$^2$ IV day 1 + prednisone 60 mg/m$^2$ PO days 1-4.
VCAP[1]: vincristine 1 mg/m$^2$ (maximum 1.5 mg) IV + cyclophosphamide 125 mg/m$^2$ PO days 1-4 + doxorubicin 30 mg/m$^2$ IV day 1 + prednisone 60 mg/m$^2$ PO days 1-4.
PCB[1]: Peptichemio 1 mg/kg day 1 + cycophosphamide 15 mg/kg day 20 + BCNU 1 mg/kg day 29.
VCCM[1]: Vincristine 0.03 mg/kg IV (max 2 mg) day 1 + carmustine (BCNU) 0.5 mg/kg IV on day 1 + cyclophosphamide 10 mg/kg IV day 1 + melphalan 0.25 mg/kg PO days 1-4.
VAD[1]: vincristine 0.4 mg/m$^2$ IV (continuous infusion) days 1-4 + doxorubicin 9 mg/m$^2$ IV (continuous infusion) days 1-4 + dexamethasone 40 mg PO days 1-4.
VAD[2]: vincristine 0.4 mg/m$^2$ IV (continuous infusion) days 1-4 + doxorubicin 9 mg/m$^2$ IV (continuous infusion) days 1-4 + dexamethasone 40 mg IV days 1-4.
VND: vincristine 0.4 mg/m$^2$ IV (continuous infusion) days 1-4 + mitoxantrone 3 mg/m$^2$ IV (continuous infusion) days 1-4 + dexamethasone 40 mg IV days 1-4.MCBP: melphalan 8 mg/m$^2$ PO day 1 + cyclophosphamide 300 mg/m$^2$ IV day 1 + carmustine 100 mg/m$^2$ IV day 1 + 6-week tapering course of prednisone beginning at a dose of 0.8 mg/kg for 14 days, with reductions to 0.4 mg/kg days 15-28, and 0.2 mg/kg days 29-42. Sep-MCBP: melphalan 16 mg/m$^2$ PO day 1 + cyclophosphamide 600 mg/m$^2$ IV day 22 + carmustine 150 mg/m$^2$ IV day 43 + 6-week tapering course of prednisone beginning at a dose of 0.8 mg/kg for 14 days, with reductions to 0.4 mg/kg days 15-28, and 0.2 mg/kg days 29-42.
MCBPA: melphalan 8 mg/m$^2$ PO day 1 + cyclophosphamide 300 mg/m$^2$ IV day 1 + carmustine 100 mg/m$^2$ IV day 1. Doxorubicin 45 mg/m$^2$ IV was administered 3 weeks after this therapy in alternate treatment courses (days 85, 190, 295, and 400) + 6-week tapering course of prednisone beginning at a dose of 0.8 mg/kg for 14 days, with reductions to 0.4 mg/kg days 15-28, and 0.2 mg/kg days 29-42.
DEX[1]: Dexamethasone 40 mg/d IV for 4 days beginning on days 1, 9, and 17 by 2 cycles of 6 weeks and 40 mg/d IV at day 1 by 10 cycles of 6 weeks.
DEX[2]: melphalan 9 mg/m2 PO days 1-4 + dexamethasone 20 mg/m$^2$ PO days 1-4 and 9-12 every 4 weeks.
DEX[3]: melphalan 9 mg/m2 PO days 1-4 + dexamethasone 40 mg PO days 1-4 and 14-15.
M-DEX[1]: MP[5] and DEX[1] schema at the same time.
DEX-IFN: IFN alfa-2b 3.0 MU SC 3 times weekly + DEX1 schema. The IFN was started with dexamethasone and stopped on day 42 of the last dexamethasone cycle.
TD[1]: thalidomide 200 mg PO days 1-4 + dexamethasone 40 mg days 1-4.

**Annex 2.** Assessment of the risk of bias in RCTs included in the review.

| Study | Sequence generation | Allocation concealment | Blinding of participants, personnel and outcome assessors | Incomplete outcome data/withdrawals | Free of selective reporting | Other sources of bias/commentaries | Overall Risk |
|---|---|---|---|---|---|---|---|
| Blade 1990 | Unclear | Unclear | No | Unclear | Unclear | A number of patients were not evaluable for response to therapy. Adverse events were not reported. | Unclear |
| Blade 1993 | Unclear | Unclear | No | Unclear | Unclear | Yes | Unclear |
| Boccadoro 1991 | Unclear | Unclear | No | Unclear | Unclear | Hematological and non-hematological adverse events were not reported. | Unclear |
| Cavo 2002 | Unclear | Unclear | No | Unclear | Unclear | Yes | Unclear |
| Cooper 1986 | Unclear | Unclear | No | No | Unclear | Yes | No |
| Facon 2005 | Yes | Unclear | No | Yes | Unclear | Yes | Unclear |
| Facon 2008 | Unclear | Unclear | No | Yes | Unclear | Yes | Unclear |
| Gulbrandsen 2008 (abst.) | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Hamsen 1985 | Yes | Unclear | No | Unclear | Unclear | Yes | Unclear |
| Hernández 2004 | Unclear | Unclear | No | Yes | Unclear | Yes | Unclear |
| HJORT 1990 | Unclear | Unclear | No | Unclear | Unclear | Yes | Unclear |
| Hulin 2009 | Unclear | Yes | Unclear | Yes | Unclear | Baseline characteristics were well balanced except for gender. | Unclear |
| Kildahl-Andersen 1988 | Unclear | Unclear | No | Unclear | Unclear | Adverse events were not reported. | Unclear |
| Ludwig 2008 | Yes | Yes | No | Yes | Unclear | Yes | Yes |
| Osterborg 1989 | Unclear | Unclear | No | Unclear | Unclear | Yes | Unclear |
| Palumbo 2006 | Yes | Yes | No | Unclear | Unclear | Hematological and non-hematological adverse events were not reported for each group. | Yes |
| Pavlovsky 1984 | Unclear | Unclear | No | Unclear | Unclear | No sample size calculation. | Unclear |
| Pönisch 2006 | Unclear | Unclear | No | Yes | Unclear | Every adverse event was reported (i.e. leucopenia, anemia, thrombocytopenia), however they were not be summarized as “hematological toxicity”. | Unclear |
| Salmon 1983 | Unclear | Unclear | No | Unclear | Unclear | Yes | Unclear |
| San Miguel 2008 | Unclear | Unclear | No | Unclear | Unclear | Every adverse event was reported, however they were not be summarized as “hematological toxicity”. | Unclear |
| Shustik, 2006 | Yes | Yes | No | Yes | Unclear | Yes | Yes |
| Tribalto 1985 | Yes | Unclear | No | No | Unclear | Hematological and non-hematological adverse events were not adequately reported. | Unclear |
| Wijermans 2008 (abst.) | Unclear | Unclear | No | Unclear | Unclear | Unclear | Unclear |

Abst: Abstract.

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