This 13th biannual report of the Cochrane Hematological Malignancies Group highlights recently published randomized controlled trials (RCTs) in the field of hemato-oncology, covering the publication period from July 2010 to February 2011. Implications for clinical practice and methodological aspects are the main principles for selecting trials for this report. Studies were identified by an electronic search of MEDLINE using a broad search filter that covers all topics in hemato-oncology combined with a highly sensitive search filter for randomized trials (Cochrane Handbook for Systematic Reviews of Interventions). The electronic search of the OVID MEDLINE database was conducted on February 28, 2011. In this summary of key features of recent RCTs, we focus on multiple myeloma (MM). Of the 62 identified RCTs, 15 evaluated different treatment approaches in patients with MM. Five of these 15 trials are selected and presented in detail [three in long version (1–3) and two in short version (4,5)]. Three further RCTs of clinical importance are also presented in less detail (6–8).

After a short overview of the clinical relevance and the selection of patients for the trials, we discuss important methodological aspects of each trial, for example, randomization, loss to follow-up, and statistical analysis. We also discuss the results of the primary efficacy endpoints and safety analysis. The main objective of this summary report is to provide busy practitioners with easily accessible and interpretable information about RCTs for MM. In addition, we give a summary of the latest Cochrane reviews and protocols developed by the Cochrane Haematological Malignancies Group.

Published Trials in MM patients

Clinical Background

MM is a relatively common disease, accounting for approximately 13% of all hematologic malignancies. MM is characterized by neoplastic proliferation of plasma cells in the bone marrow, which leads to marrow failure and bone destruction (9). MM has an incidence rate of 4.5–6.0 cancers per 100 000 people per year. The median age at diagnosis ranges from 63 to 70 years of age (10,11). The presence or absence of symptoms, that is, anemia, hypocalcemia, renal insufficiency, or bone lesions, is the main determinant for therapeutic intervention (10,12). Patients with smoldering MM or monoclonal gammopathy of undetermined significance do not require treatment (10,12), whereas symptomatic MM has to be treated with systemic anti-
myeloma therapy. For patients younger than 65–75 years of age and older patients with good general health and no comorbid conditions, high-intensity chemotherapy with autologous hematopoietic cell transplantation is the standard treatment (10,12).

For patients who are not considered to be candidates for a high-dose chemotherapy regimen with or without transplantation, because of age or having a comorbidity, melphalan plus prednisone (MP) has been the standard treatment for more than 40 years (10,12,13). In addition, there were several further regimens, for example, dexamethasone alone, thalidomide plus dexamethasone, vincristine plus doxorubicin and dexamethasone (12), which also have been recommended as alternative treatments for these patients. However, in recent years, two treatment approaches—MP plus thalidomide (14,15) and MP plus bortezomib (16)—have demonstrated improved anti-myeloma, and the study showed and improved overall survival (OS) efficacy compared with MP alone. Both regimens are recommended by clinical guidelines as standard of care for the treatment of patients with MM who are ineligible for transplantation (10,12,13). Another recommended treatment option is low-dose dexamethasone plus lenalidomide, which demonstrated improved complete response (CR) and overall response rates (ORRs) compared with high-dose dexamethasone plus lenalidomide (10,12,13,17). Below, we discuss currently published trials that examined different treatment approaches of lenalidomide, bortezomib, and thalidomide.

**Trial 1: Lenalidomide and High-Dose Dexamethasone Compared With Dexamethasone as Initial Therapy for Multiple Myeloma: A Randomized Southwest Oncology Group trial (S0232)**


**Contribution.**

The study enrolled 198 patients and did not reach the projected enrollment of 500 patients because the Data and Safety Monitoring Committee recommended early study closure. The trial included newly diagnosed, transplantation-ineligible and transplantation-denying adult patients with symptomatic MM. Patients were randomly assigned to three courses of lenalidomide plus dexamethasone (LD) or three courses of dexamethasone plus placebo (D) and were administered maintenance therapy with LD or D, respectively. Patients with progressive disease were encouraged to crossover from D to LD. Patients with progressive disease in the LD arm were removed from the study protocol.

The study protocol was amended after the first 21 patients were randomly assigned to a treatment arm because a statistically significant incidence of thromboembolic events in the LD arm was observed (eight of 12 patients receiving LD had thromboembolic events vs 0 of nine patients receiving D, \( P = .002 \)). All subsequently randomly assigned patients received aspirin prophylaxis, but the excess of thromboembolic events in patients receiving LD persisted until the early closure or the trial (thromboembolic events were observed in 18 (19%) of 97 patients in the LD arm vs six (6%) of 95 patients in the D arm, \( P = .01 \)).

The median follow-up time was not reported. Patients treated with LD had a statistically significantly increased ORR (LD arm ORR = 78% vs D arm ORR = 48%, \( P < .0001 \)) and progression-free survival (PFS) (hazard ratio [HR] or \( P \) value not provided) compared with the patients in the D arm. However, the increased ORR and PFS among patients in the LD arm did not lead to improved OS, and a higher frequency of severe adverse events was observed in these patients.
**Implication for Practice.**

Both the early closure of a study and crossover among patients into a different study arm may cause severe bias in treatment outcomes. Therefore, outcomes in this study should be interpreted very carefully because of methodological shortcomings. An alarming incidence of thromboembolic events led to the recommendation of administration of a general thromboprophylaxis to patients. Although the results of this trial indicated improved ORR and PFS for patients receiving LD, the treatment was also associated with a higher frequency of severe adverse events, particularly, neutropenia, lymphocytopenia, infections, and thromboembolic events. The value of LD regarding OS remains unclear because of the high number of patients who crossed over from D to LD.

**Most Interesting Feature.**

This trial was closed early because of the high incidence of thromboembolic events in the LD arm. This statistically significantly higher incidence of these events persisted after the amendment of the protocol, which recommended aspirin prophylaxis for all patients.

**Table 1. Key study features for Zonder et al. (1) * **

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size calculation</td>
<td>83% power for the detection of 33% improvement in PFS (n = 500); The Data and Safety Monitoring Committee recommended early study closure and sample size was smaller (n = 198).</td>
</tr>
<tr>
<td>Randomization</td>
<td>Stratified by international staging system (stage 1 vs 2 vs 3) and Zubrod performance status (0 or 1 vs 2 or 3); Generation of allocation sequences was not reported.</td>
</tr>
<tr>
<td>Blinding</td>
<td>After recommended early closure, the original treatment allocation was unblended and open-label LD was made available to all patients.</td>
</tr>
<tr>
<td>Setting</td>
<td>Not reported</td>
</tr>
<tr>
<td>Patients</td>
<td>Transplantation-ineligible or transplant-denying patients with symptomatic disease and a measurable M-protein who were aged ≥18 y with a performance status &lt;3 (unless resulting from myeloma).</td>
</tr>
<tr>
<td>Study drug regimen</td>
<td>Induction therapy: Study arm 1 (LD) = three 35-d cycles of dexamethasone 40 mg/d (days 1–4, 9–12, and 17–20) plus lenalidomide at 25 mg/d for 28 d; Study arm 2 (D) = three 35-d cycles of dexamethasone 40 mg/d (days 1–4, 9–12, and 17–20) plus placebo. Maintenance therapy: Study arm 1 = 28-d cycles of dexamethasone 40 mg/d (days 1–4 and 15–18) plus lenalidomide 25 mg/d for 21 d; Study arm 2 = 28-d cycles of dexamethasone 40 mg/d (days 1–4 and 15–18) plus placebo in repeating 28-d cycles. Further recommendations: Both treatment arms were continued until PD or unacceptable toxicity. After a high incidence of thromboembolic events in the first 21 patients, all subsequent patients received aspirin (325 mg/d). On PD, patients on D could cross over to open-label LD.</td>
</tr>
<tr>
<td>Patient flow</td>
<td>No. of patients randomly assigned to treatment = 198 (1:1); Total No. of patients analyzed = 192; No. of patients per arm: 97 in LD arm; 95 in D arm; No. of discontinuations: 17 in LD arm; 15 in D arm; No. of patients who crossed over = 42 of 95 patients crossed from D to LD.</td>
</tr>
</tbody>
</table>
Duration of follow-up
Median follow-up after induction therapy = 47.2 mo.

Analysis
Authors stated that all analyses were conducted according to the intention-to-treat principle.

Outcomes
Primary outcome = PFS; Secondary outcomes = OS, response rates (ORR, CR rate, and PR rate), and safety.

Results
PFS at 3 y: 52% in the LD arm vs 32% in the D arm, hazard ratios and \( P \) value not provided; OS at 3 y: 79% in the LD arm vs 73% in the D arm, hazard ratios and \( P \) value not provided; ORR: Statistically significant difference was found among the LD arm (78%) vs the D arm (48%) \( (P < .0001) \); CR rate: 26% in the LD arm vs 4% in the D arm, \( P \) value not provided; PR: 15% in the LD arm vs 32% in the D arm, \( P \) value not provided; Safety: differences among the LD arm vs the D arm were observed for the cumulative rate of grade 3 or 4 adverse events (21% for the LD arm vs 5% for the D arm; \( P = .0009 \)); Neutropenia (22% for the LD arm vs 5% for the D arm); Thrombocytopenia (7% for the LD arm vs 3% for the D arm); Lymphocytopenia (10% for the LD arm vs 3% for the D arm); Anemia (6% for the LD arm vs 5% for the D arm); Infections (16% for the LD arm vs 12% for the D arm); Venous thromboembolism (19% for the LD arm vs 6% for the D arm); Fatigue (19% for the LD arm vs 12% for the D arm); Depression (11% for the LD arm vs 8% or the D arm); Muscle weakness (9% for the LD arm vs 3% for the D arm); Hypocalcemia (7% for the LD arm vs 2% for the D arm); Hypokalemia (6% for the LD arm vs 1% for the D arm); Details regarding discontinuations because of adverse events not provided.

Potential conflict of interest
Four of the 10 authors (including first, second, and last author) declared conflicts of interest because they received research funding from Celgene and Millenium and honoraria from Celgene.

Funding source
The study was supported by Celgene Corporation and by the National Cancer Institute, Department of Health and Human Services.

*CR = complete response; D = high-dose dexamethasone (study arm 2); LD = lenalidomide and high-dose dexamethasone (study arm 1); PD = progressive disease; PFS = progression-free survival; PR = partial response; OS = overall survival; ORR = overall response rate.

†Six patients were ineligible: three patients did not meet baseline disease characteristics, two patients had inadequate organ function, and one patient had a prior malignancy.

**Trial 2: Thalidomide Plus Bortezomib and Prednisone vs Melphalan Plus Bortezomib and Prednisone for First-Line Treatment and Thalidomide Plus Bortezomib vs Melphalan Plus Bortezomib For Maintenance Therapy**


**Contribution.**

This randomized, multicenter open-label trial enrolled 260 patients. It included previously untreated adult MM patients aged 65 years or older. The trial examines the efficacy and safety of bortezomib plus thalidomide and prednisone (VTP, \( n = 130 \)) compared with bortezomib plus melphalan and prednisone (VMP, \( n = 130 \)). Patients who completed the induction therapy were subsequently randomly assigned to 3-year maintenance therapy with either bortezomib plus thalidomide (VT) or bortezomib plus prednisone (VP). Bortezomib was mainly administered once
a week rather than twice a week, as it was done by San Miguel et al. (16). Furthermore, the number of induction therapy cycles was reduced from nine to six (16). This less-intensive bortezomib regimen was given in both arms of the trial.

After a median follow-up of 32 months after patients were randomly assigned to induction therapy, CR, ORR, PFS, and OS were similar for both induction treatment arms. Regarding adverse events, treatment with VTP caused a statistically significantly increased number of serious adverse events (SAEs) and discontinuations because of SAEs compared with treatment with VMP.

After induction therapy, 178 patients were randomly assigned to receive VT (n = 91) or VP (n = 87) as maintenance therapy. CR, PFS, OS, severe adverse events, discontinuation of treatment because of adverse events, and the number of deaths were similar in the VT and VP maintenance therapy arms. Mateos et al. (3) concluded that the outcome of VT maintenance was independent of the type of induction therapy administered. Further data of subgroup analyses were not provided.

Implication for Practice.

The aim of this study was to investigate if administration of less-intensive bortezomib could maintain efficacy and reduce the toxic effects. Therefore, the frequency of bortezomib administration and the total number of induction therapy cycles was reduced.

Mateos et al. (3) investigated VT compared with VMP. It was powered to investigate efficacy by measuring CR. However, results are similar in terms of PFS and OS, but this cannot be interpreted as proven similar efficacy of both treatments. These results might have been caused by the small number of patients (n = 260) and/or a small number of observed events (number of events regarding PFS or OS were not reported). Furthermore, VTP showed an increased number of SAEs and discontinuations because of SAEs. Regarding maintenance therapy, the comparison of VT and VP did not show any advantages or disadvantages of one treatment vs the other.

Most Interesting Feature.

The trial investigated two less-intensive VTP regimens in elderly untreated patients with MM but did not provide a direct comparison with the effective VTP regimen that was investigated by San Miguel et al. (16). Further studies designed to examine differences in PFS and OS are needed to clarify the efficacy of VTP compared with VMP.

Table 2. Key study features for Mateos et al. (3) *

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size calculation</td>
<td>Sample size (n = 260) was determine by a calculation for two randomizations; First randomization for induction therapy was aimed to achieve 20% difference in the CR rate after induction; Second randomization for maintenance therapy was aimed to improve the CR rate by ≥15% after maintenance.</td>
</tr>
<tr>
<td>Randomization</td>
<td>Generation of allocation sequences was done by a computerized random number generator (randomization was communicated via a web-based registration)</td>
</tr>
<tr>
<td>Blinding</td>
<td>Open label, with no blinding of the participants those giving treatment, assessing outcomes, or analyzing data.</td>
</tr>
<tr>
<td>Setting</td>
<td>63 Spanish centers.</td>
</tr>
</tbody>
</table>
Patients

Newly diagnosed and/or untreated patients aged ≥65 y with an Eastern Cooperative Oncology Group score of 0–2 who were symptomatic with measurable MM (measurable defined as serum monoclonal protein >10 g/L or urine monoclonal protein ≥0.2 g/d); hemoglobin of >80 g/L; latelet count of ≥50×10^9/L; absolute neutrophil count of >1.0×10^9 cells/L; no renal dysfunction; and no peripheral neuropathy ≥ grade 2.

Study drugs

Induction regimen 1 (VMP): one 6-wk cycle of bortezomib at 1.3 mg/m² (twice weekly), melphalan at 9 mg/m² (once daily, days 1–4), and prednisone at 60 mg/m² (once daily, days 1–4); followed by five 5-wk cycles of bortezomib at 1.3 mg/m² (once weekly), melphalan at 9 mg/m² (once daily, days 1–4), and prednisone at 60 mg/m² (once daily, days 1–4). Induction regimen 2 (VTP): one 6-wk cycle of bortezomib at 1.3 mg/m² (twice weekly), prednisone at 60 mg/m² (once daily, days 1–4), and thalidomide at 100 mg (once daily); followed by five 5-wk cycles of bortezomib at 1.3 mg/m² (once weekly), prednisone at 60 mg/m² (once daily, days 1–4), and thalidomide at 100 mg (once daily); Maintenance regimen 1 (VP): bortezomib at 1.3 mg/m² (days 1, 4, 8, and 11) every 3 mo and prednisone at 50 mg (every 48 h). Maintenance regimen 2 (VT): bortezomib at 1.3 mg/m² (days 1, 4, 8, and 11) every 3 mo, and thalidomide at 50 mg (once daily).

Patient flow

No. of patients randomly assigned for induction therapy = 260 patients (1:1 ratio of VMP vs VTP); No. of patients with a CR randomly assigned for maintenance therapy = 178 patients (1:1 ratio of VP vs VT); No. of patients analyzed for induction therapy = 260 patients, with 130 patients in the VMP arm and 130 patients in the VTP arm; No. of patients discontinuing induction therapy = 39 of 130 patients discontinued VMP (reasons = seven deaths, one lung neoplasia, six disease progressions, 15 toxic effects, and 10 withdrawn consents), and 43 of 130 patient discontinued VTP (reasons = seven deaths, seven disease progressions, 22 toxic effects, and seven withdrawn consents); No. of patients analyzed for maintenance therapy = 178 patients, with 91 patients in the VP arm (47 VMP-VT, 44 VMP-VP) and 87 patients in the VT-arm (44 VTP-VT, 43 VTP-VP); No. of patients who discontinued maintenance therapy = 54 of 91 patients received VP (29 VMP-VT, 25 VMP-VP, discontinuation reasons not reported), and 43 of 87 received VT (26 VTP-VT, 17 VTP-VP, discontinuation reasons not reported).

Duration of follow-up

Median follow-up from first randomization = 32 mo (interquartile range = 25–38 mo); Median follow-up from second randomization = 22 mo (interquartile range = 17–29 mo).

Analysis

Intention-to-treat principle

Outcomes

Primary outcome = CR; Secondary outcomes = ORR, PFS, OS, and safety.

Results

CR rate after induction therapy was 26 (20%) of 130 patients in the VMP arm and 36 (28%) of 130 patients in the VTP arm; CR rate after maintenance therapy was 34 (39%) of 91 patients in the VP arm and 40 (44%) of 87 patients in the VT arm; ORR induction therapy was 104 (80%) of 130 patients in the VMP arm and 105 (81%) of 130 patients in the VTP arm; ORR for
maintenance therapy was not provided; The PFS for induction therapy was similar between the VMP (median survival = 34 mo) and VTP (median survival = 25 mo) arms (HR = 1.2, 95% CI = 0.9 to 1.7; \( P = .1 \)); The PFS for maintenance therapy was similar between the two arms (HR = 1.4, 95% CI = 0.8 to 2.1; \( P = .1 \)); The OS for induction therapy at 3 y was similar between the VMP (76%) and VTP (65%) arms (HR = 1.2, 95% CI = 0.7 to 1.9; \( P = .3 \)); The OS for maintenance therapy between the two arms was similar (HR = 1.2, 95% CI = 0.6 to 2.4; \( P \) value not provided); Differences between the arms in safety outcomes during induction therapy: related SAEs = 15% for the VMP arm vs 31% for the VTP arm (\( P = .01 \)), patients discontinuing because of SAEs = 12% for the VTP arm vs 17% for the VMP arm (\( P = .03 \)), deaths = 5% for the VTP arm vs 5% for the VMP arm (\( P = .8 \)); Differences in safety outcomes during maintenance therapy: patients discontinuing because of SAEs = 8% for the VT arm vs 5% for the VP arm (\( P = .6 \)), deaths = 1% for the VT arm vs 1% for the VP arm (\( P = .8 \)).

Potential conflicts of interest

Ten (including first, second, and last author) of the 29 authors declared conflicts of interest because they received honoraria from Celgene and Ortho-Biotech or served on the speaker’s bureau for Millennium, Celgene, and/or Ortho-Biotech.

Funding source

This study was funded by Celgene, Johnson & Johnson, the Spanish Program for the Treatment of Hematologic Diseases, and Fondo de Investigación Sanitaria.

*HR = hazard ratio; MM = multiple myeloma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SAE = serious adverse event; VP = bortezomib and prednisone; VT = bortezomib and thalidomide; VMP = bortezomib, melphalan, and prednisone; VTP = bortezomib, prednisonse, and thalidomide.

**Trial 3: Melphalan and Prednisone Plus Thalidomide or Placebo in Elderly Patients With Multiple Myeloma**


**Contribution.**

This trial enrolled 363 patients of the initially estimated 800. The reasons for under-recruiting were not provided. The study by Waage et al. (2) is a double-blind placebo-controlled trial that included newly diagnosed, transplantation-ineligible, or transplantation-denying adult patients with symptomatic MM. The patients were randomly assigned to receive either melphalan-prednisone and thalidomide (MPT) or melphalan-prednisone and placebo (MPP). After a median follow-up time of 42 months, patients showed no statistically significant difference in terms of OS and PFS between the treatment arms. Patients treated with MPT had two times more nonhematologic adverse events (40% patients in MPT arm vs 19% patient in MPP arm) and discontinued therapy more often because of adverse events (32% patients in MPT arm vs 10% patients in MPP arm). The median survival was not statistically significant shorter in the MPT arm with 29 months compared with 32 months in the MPP arm. Furthermore, the authors of the article discussed a slight, not statistically significant, increase in mortality of patients with thalidomide treatment within the first 6 months. In this period, there were 35 deaths in the MPT arm vs 21 deaths in the MPP arm. The main part of these patients was older than 75 years. In the
MPT arm, 65% of patients who died in the first 6 months were at least 75 years old compared with 52% in the MPP arm. A similar effect was detectable in the results presented by Wijermans et al. (4) (publication discussed below). Quality of life was assessed at 3 and 12 months, but the provided data and results are not sufficient to validate the authors’ conclusion.

**Implication for Practice.**

Administration of thalidomide in addition to MPP showed no statistically significant improvement compared with MP plus placebo in terms of OS, PFS, or quality of life. However, patients treated with MPT had two times more nonhematologic adverse events and discontinued therapy three times more often because of adverse events. Furthermore, patients older than 75 years of age might have an increased risk of early mortality when receiving MPT, which should be taken into consideration during individually adapted patient treatment.

**Most Interesting Feature.**

This trial and the study presented by Wijermans et al. (4) (discussed below) showed no differences regarding the provided chemotherapeutical regimens (besides the placebo administration), follow-up period, and sample size. However, it had surprisingly different outcome results in terms of PFS (Waage et al. (2): no statistical differences; Wijermans et al. (4): HR = 0.65, 95% CI = 0.49 to 0.88; \( P = 0.006 \)) and median survival (Waage et al.: 29 months in the MPT arm and 32 months in the MPP arm; Wijermans et al.: 40 months with MPT vs 31 months with MPP). Reported differences of these trials apply to the study population: Waage et al. (2) included patients who were not eligible for high-dose treatment with autologous stem cell support; Wijermans et al. (4) included patients older than age 65 years and WHO performance status of 0–3. Waage et al. (2) enrolled more patients older than 75 years (39% vs 31%) and more patients with a performance status of 3 or more (67% vs 4%) compared with Wijermans et al. (4). Therefore, further trials should examine whether elderly patients or patients with a low performance status benefit from a treatment with additional thalidomide.

**Table 3.** Key features for Waage et al. (2) *

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size calculation</td>
<td>Sample size (n = 800 patients) was on the basis of OS (aimed to detect HR of 1.4, this corresponds with median survival of 28 mo [MPP] vs 40 mo [MPT], with 80% power). However, the study recruited only 363 patients (179 MPP, 184 MPT)—reasons were not reported.</td>
</tr>
<tr>
<td>Randomization</td>
<td>Stratified by: WHO performance status ( \leq 2 \text{ or } 3–4 ) and ( \beta_2 )-microglobulin (&lt; 2.6 \text{ mg/L, } &gt; 2.6 \text{ mg/L, or unknown} ). Generation of allocation sequences: centralized and performed by telephone call or fax.</td>
</tr>
<tr>
<td>Blinding</td>
<td>Double-blind study; evaluation of outcomes was performed without knowledge of treatment arm.</td>
</tr>
<tr>
<td>Setting</td>
<td>Recruited from 48 hospitals in Norway, Sweden, and Denmark.</td>
</tr>
<tr>
<td>Patients</td>
<td>Previously untreated symptomatic MM patients with a performance status WHO 0–4 and a Durie–Salmon stage I–III who were not eligible for high-dose treatment with autologous stem cell support were eligible. Excluded: women of childbearing age; patients with psychiatric disease; patients expected to survive less than 3 mo; patients who did not cooperate or who refused consent.</td>
</tr>
<tr>
<td>Study drug</td>
<td>MPT: melphalan at 0.25 mg/kg, prednisone at 100 mg (once daily for 4 d every</td>
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*This table is part of the text and not included in the provided image.*
6 wk). Cycles of treatment were continued until plateau phase. Thalidomide was administered at 200 mg (once daily for 1 wk) followed by 400 mg (once daily). MPP: melphalan at 0.25 mg/kg, prednisone 100 mg (once daily for 4 d every 6 wk). Cycles of treatment were continued until plateau phase. Placebo at 200 mg (once daily for 1 wk) followed by 400 mg (once daily). The dose was maintained until the plateau phase and thereafter continued at 200 mg daily. Further recommendations: Dose reduction was allowed because of side effects. The protocol was prescribed to repeat the induction treatment at the time of the first relapse and continued maintenance treatment until the second relapse.

### Patient flow

- No. of patients randomly assigned = 363 patients (1:1 ratio MPT vs MPP); No. of patients analyzed for survival = 357 patients, with 182 patients in the MPT arm and 175 patients in the MPP arm; No of patients discontinuing treatment = 79 of 182 patients discontinued MPT (reasons: 59 because of toxicity, four because of patient wish, three never started, five because of lack of compliance, and eight because of unknown causes), and 35 of 175 patients discontinued MPP (reasons: 18 because of toxicity, two because of patient wish, three never started, three because of lack of compliance, two because of unconfirmed progressive disease, seven because of unknown causes).

### Duration of follow-up

- Median follow-up = 42 mo

### Analysis

- Intention-to-treat principle

### Outcomes

- Primary outcome = OS; Secondary outcomes = response rates, PFS, health-related quality of life, safety.

OS was similar between MPT (median survival = 29 mo) and MPP arms (median survival = 32 mo), HR not reported, \( P = .16 \); PFS was similar between MPT (median survival = 15 mo) and MPP arms (median survival=14 mo), HR and \( P \) not reported; ORR: 57% MPT arm and 40% MPP arm; CR: 13% MPT arm and 4% MPP arm; PR: 34% MPT arm and 33% MPP arm; Health-related quality of life (QLQ-C30) was assessed at 3 mo (82% replied in the MPT and 90% in the MPP arm) and at 12 mo (50% replied in the MPT and 62% replied in the MPP arm). Quality of life was improved in both treatment arms after initiation of treatment. Besides a marked increase in constipation among patients in the MPT arm (\( P = .001 \)), both arms are similar regarding assessed quality of life measures (the article did not provide data to verify these statements); Differences between the arms in safety outcomes (\( P \) values not provided): Cumulative rate of all nonhematologic AE = 40% for the MPT arm vs 19% for the MPP arm, discontinuations because of AE = 59 patients of the MPT arm vs 18 patients of the MPP arm, infections grade 3 or 4 = 15% for the MPT arm vs 10% for the MPP arm, cardiologic toxicity grade 3 or 4 = 7% for the MPT arm vs 5% for the MPP arm, non-neuropathy neurological toxicity grade 3 or 4 = 8% for the MPT arm vs 2% for the MPP arm, neuropathy grade 3 or 4 = 6% for the MPT arm vs 1% for the MPP arm, constipation grade 3 or 4 = 6% for the MPT arm vs 3% for the MPP arm, thromboembolic events grade 3 or 4 = 8% for the MPT arm vs 8% for the MPP arm.
Feature | Details
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Potential conflict of interest | Five of the 25 named authors (including the first and second authors) are consultants of at least one of the following companies: Janssen Cilag, GenMab, Schering-Plough, Bristol-Myers Squibb, Merck Serono. Another author was employed by Roche after the study was published.
Funding source | The trial was granted by the Norwegian Cancer Society and the Norwegian Research Council. Thalidomide and placebo were provided by Gruenenthal Gmbh, Aachen.

*CR = complete response; MPP = melphalan and placebo; MPT = melphalan and thalidomide; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; WHO = World Health Organization.

**Trial 4: Phase III Study of the Value of Thalidomide Added to Melphalan Plus Prednisone in Elderly Patients With Newly Diagnosed Multiple Myeloma: The HOVON 49 Study**


**Contribution.**

This was an open-label multicenter trial. It included newly diagnosed patients with MM older than 65 years of age. These were randomly assigned to eight cycles of melphalan 0.25 mg/kg and prednisone 1 mg/kg (which were administered daily for 5 days every 4 weeks) (MP, N = 173) or eight cycles of MP with thalidomide 200 mg/d (MPT, N = 171). Only patients in the MPT arm received maintenance therapy (thalidomide 50 mg/d, N = 65). That was administered until relapse. The trial was stopped after randomization of 344 patients instead of 420 estimated patients, because two other publications (14,15) indicated a superior effect of MPT compared with MP alone. Of these 344 patients, 11 were excluded because they did not comply with the entry criteria.

After a median follow-up of 39 months, patients with MPT showed a statistically significant improved PFS (multivariate regression analysis: HR = 0.65, 95% CI = 0.49 to 0.88; *P* = 0.006). There was no statistical difference in OS (multivariate regression analysis: HR = 0.82, 95% CI = 0.61 to 1.10; *P* = 0.19). Most interesting, the figure displaying the OS curve, only representing patients older than 75 years of age, suggests a slight increase in mortality in MPT arm during the first months. This was seen likewise for patients older than 75 years of age in the Waage et al. (2) trial (publication discussed above). As expected, MPT was less tolerated than MP (treatment discontinuations: 37% vs 10%; adverse events grade 3 or 4: 50% vs 29%, particularly neurological toxicities 23% vs 4% and thrombosis 3% vs 0%). Data regarding treatment-related mortality were not provided. According to the authors of the study, 285 of 333 eligible patients participated in the quality of life study that will be presented separately. So far, they state that there were no subscales indicating a favorable or unfavorable influence of thalidomide.

**Implications for Practice.**

This trial showed statistically significant improved PFS and response rates for patients receiving MPT compared with MP alone. This did not lead to a statistically significant improvement of OS. Furthermore, treatment with MPT caused more severe adverse events (*P* values not provided) and the discontinuation of treatment because of toxicity was four times more likely in patients receiving MPT compared with those in the MP arm. [Please consider a further discussion of these results stated above at “Most interesting feature” of Waage et al. (2)]
Trial 5: First-Line Treatment With Zoledronic Acid as Compared With Clodronic Acid in Multiple Myeloma (MRC Myeloma IX): A Randomised Controlled Trial


Contribution.

Bisphosphonates were developed mainly to impair malignant osteolysis; however, preclinical studies suggest that bisphosphonates might have inherent anticancer activities (18). The study by Morgan et al. (5) was a randomized, open-label multicenter trial comparing two bisphosphonates, that is, clodronic acid (daily oral dose of 1600 mg) and zoledronic acid (4 g given intravenously every 3–4 weeks). The bisphosphonates were given in addition to intensive chemotherapy (ie, four to six 21-day cycles of cyclophosphamide, vincristine, doxorubicin, and dexamethasone or cyclophosphamide, thalidomide, and dexamethasone) or nonintensive chemotherapy (ie, six to nine 28-day cycles of MP or attenuated cyclophosmamide, thalidomide, and dexamethasone).

The trial enrolled 1970 adult patients with newly diagnosed MM. Of these patients, 1960 were eligible for intention-to-treat analysis. The zoledronic acid group (n = 981) included 555 patients receiving intensive chemotherapy and 426 patients receiving on nonintensive chemotherapy. The clodronic acid group (n = 979) included 556 patients receiving intensive chemotherapy and 423 patients receiving nonintensive chemotherapy. After induction therapy, 820 patients without progressive disease were randomized again to receive thalidomide or no further treatment as maintenance therapy. Both bisphosphonates and maintenance therapy were given continuously at least until disease progression. Mhaskar et al. (19) reported a systematic review with meta-analysis and indirect comparison that did not reveal the superiority of any particular type of bisphosphonate compared with others in terms of OS or PFS (19). Despite the findings, patients of the study by Morgan et al. (5) treated with zoledronic acid showed statistically significantly increased PFS (median PFS = 19.5 months for zoledronic acid vs 17.5 months for clodronic acid, HR = 0.88, 95% CI = 0.80 to 0.98; P = .0179) and OS (median OS = 50.0 months for zoledronic acid vs 44.5 months for clodronic acid, HR = 0.84, 95% CI = 0.74 to 0.96; P = .0118) compared with patients receiving clodronic acid, after a median follow-up of 3.7 years. However, the direct comparison of the treatment with zoledronic acid caused a statistically significantly increase in the percentage of SAEs observed in patients given zoledronic acid (55%) vs clodronic acid (49%) (P < .0001), particularly thrombotic events (16% for zoldronic acid vs 12% for clodronic acid, P = .01) and osteonecrosis of the jaw (4% for zoledronic acid vs <1% for clodronic acid, P < .0001). Data regarding treatment-related mortality or results with respect to the different maintenance therapy approaches were not provided.

Implications for Practice.

This was an innovative RCT with newly diagnosed adult MM patients. It examined the anticancer properties of two bisphosphonates, clodronic acid and zoledronic acid, given in combination with intensive or nonintensive chemotherapy. It showed that zoledronic acid in addition to chemotherapy improved PSF and OS (extended median OS by approximately 5.5 months) compared with clodronic acid in addition to chemotherapy, but caused more SAEs, particularly thrombotic events, and osteonecrosis of the jaw. These findings support the hypothesis that zoledronic acid has anticancer activity in addition to the treatment benefits in bone health for patients with MM.

Other Interesting Trials

Trial 6: Reduced Treatment Intensity in Patients with Early-Stage Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a malignancy of the lymph nodes and lymphatic system with possible involvement of other organs. With an annual incidence of approximately 2–3 cancers per 100,000 inhabitants of Western countries, it is a comparatively rare disease, but it is one of the most common malignancies in young adults (20). Between 80% and 90% of HL in adults can be cured by primary chemotherapy with or without radiotherapy (6,21,22).

The study by Engert et al. (6) was a randomized, open-label multicenter trial that included 1370 newly diagnosed early-stage HL patients (clinical stage I or II). These were randomly assigned in a 1:1:1:1 ratio to one of four treatment groups: group 1 received four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 30 Gy of involved-field radiation therapy (IFRT) (n = 346); group 2 received four cycles of ABVD followed by 20 Gy of IFRT (n = 340); group 3 received two cycles of ABVD followed by 30 Gy of IFRT (n = 341); and group 4 received two cycles of ABVD followed by 20 Gy of IFRT (n = 343). After a median follow-up period of 7.5 years, different cycles of administrated chemotherapy regimens (two cycles of ABVD vs four cycles of ABVD) as well as the two doses of radiation therapy (20 Gy vs 30 Gy), freedom from treatment failure and OS were similar among the different treatment groups. Furthermore, patients who were in the most intense treatment arm of four cycles ABVD and 30 Gy IFRT had similar freedom from treatment failure (HR = 1.07, 95% CI = 0.65 to 1.77) and OS (HR = 0.85, 95% CI = 0.41 to 1.79) compared with the arm with least intense therapy of two cycles ABVD and 20 Gy IFRT. Adverse events occurred more often in patients receiving four cycles of ABVD than in those with two cycles of ABVD. These events include severe toxicity of grade III or IV (51.7% for patients receiving four cycles ABVD and 30 Gy IFRT vs 33.2% for patients receiving two cycles ABVD and 20 Gy IFRT; P < .001) and treatment-related deaths (six deaths vs one death, respectively). Furthermore, patients with the more intense therapy of 30 Gy of IFRT reported more SAEs (grade III or IV) than those who received 20 Gy (8.7% vs 2.9%, respectively; P < .001). However, the occurrence of secondary cancers among the four treatment groups, the pooled chemotherapy groups, or the pooled radiation therapy groups was similar (P = .59, .89, and .34, respectively). Data regarding further long-term toxicities such as infertility or cardiopulmonary diseases were not provided.

The results of Engert et al. (6) demonstrated that a reduced intensity of treatment with a short two-cycle chemotherapy treatment of ABVD followed by a reduced radiation of 20 Gy IFRT does not have a reduced ability to cure patients with early-stage HL. The side effects of this short-time treatment are considerably lower, and the less-intensive approach might also lead to a reduction of treatment-induced late toxicities.

**Trial 7: Addition of Rituximab to Fludarabine and Cyclophosphamide in Patients With Chronic Lymphocytic Leukaemia: A Randomised, Open-Label Phase 3 Trial**


Chronic lymphocytic leukemia accounts for 25% of all leukemia and is the most common lymphoid malignancy in Western hemisphere. The disease remains incurable with conventional chemotherapy. On the one hand, rituximab in addition to chemotherapy may be an effective treatment option for chronic lymphocytic leukemia patients with the potential of finally increasing overall survival. On the other hand, there is also a risk of serious side effects (eg, infections).

The randomized, open-label multicenter trial reported by Hallek et al. (8) enrolled 817 previously untreated patients with chronic lymphocytic leukemia (Binet stage C or active disease of Binet stages A or B). They were randomly assigned to six courses of fludarabine at 25 mg/m² per day and cyclophosphamide at 250 mg/m² per day (FC, n = 409) or six courses of FC (the same
three years after patients were randomly assigned to treatment arms, those treated with FCR showed statistically significantly increased PFS (median = 51.8 months for the FCR arm vs 32.8 months for the FC arm, HR = 0.56, 95% CI = 0.46 to 0.69, P < .0001) and overall survival (the time to 25% of patients dying was 62.5 months for the FCR arm vs 46.8 months for the FC arm, HR = 0.67, 95% CI = 0.48 to 0.92, P = .01) compared with the FC arm. As expected, FCR was less tolerated than FC (grade 3 or 4 adverse events = 76% for the FCR arm vs 63% for the FC arm). This difference in tolerability was attributed to hematologic toxicities, particularly neutropenia (34% for the FCR arm vs 21% for the FC arm) and leucocytopenia (24% for the FCR arm vs 12% for the FC arm). However, treatment-related mortality was similar among the two treatment arms (eight patients in the FCR arm and 10 patients in the FCR arm died because of toxic effects).

The main limitation of this study relates to the study population examined in the trial. The median age of included patients was 61 years of age, which is substantially lower than that of the average population of patients with chronic lymphocytic leukemia, who have a median age at disease onset of about 70 years. Therefore, the authors conclude that the population in this trial represents a selection of fairly young and physically fit patients and, as a consequence, conclusions from this trial should not be generalized to physically unfit elderly patients with chronic lymphocytic leukemia.

The report by Hallek et al. (8) was the first RCT that demonstrated an improvement in OS for physically fit chronic lymphocytic leukemia patients receiving FCR as first-line therapy. Adverse events (particularly neutropenia and leucocytopenia) occurred more often when patients were treated with FCR compared with FC but did not result in an increase in the treatment-related mortality rate.

**Trial 8: Rituximab Maintenance for 2 Years in Patients With High Tumour Burden Follicular Lymphoma Responding to Rituximab Plus Chemotherapy (PRIMA): A Phase 3, Randomised Controlled Trial**

Salles GF, Seymour JF, Offner F, et al. Lancet. 2011;377(9759):42-51 (7). Follicular lymphoma is the most common indolent and second most common non-Hodgkin lymphoma in the Western world. Prognosis and therapy of follicular lymphoma depends on the disease stage. Disseminated disease is usually incurable, whereas asymptomatic patients with no adverse prognostic features are initially only observed (watchful waiting). However, most of the diagnosed patients need systemic cytotoxic-based treatment, and their estimated median survival time is 8–10 years.

The study by Salles et al. (7) was a randomized, open-label, international multicenter trial that included 1019 adult patients with CR or partial response after first-line therapy with three different immunotherapy induction regimens (nonrandomized). Patients were randomly assigned to 2 years of rituximab maintenance therapy (375 mg/m² every 8 weeks, n = 505) or observation (n = 513). After a median follow-up of 36 months, PFS (beginning at the time of random assignment that was 6 months after the start of induction therapy) was assessed as the primary endpoint. A statistically significantly increase in PFS (HR = 0.55, 95% CI = 0.44 to 0.68, P < .0001) was observed in patients receiving rituximab maintenance therapy (74.9%) vs observation (57.6%). During this period, less than 5% of patients in each group had died, and OS was similar between the two treatment arms (HR = 0.87, 95% CI = 0.51 to 1.47). As expected, rituximab maintenance therapy led to more grade 3 or 4 adverse events than observation (24% vs 17%, respectively). Most grade 3 or 4 side effects occurring in the rituximab maintenance arm of the study were infections and neutropenia.
were neutropenia (4% for the rituximab arm vs 1% for the observation arm), neoplasia (4% for the rituximab arm vs 3% for the observation arm), and infections (4% for the rituximab arm vs 1% for the observation arm). Altogether, one patient died of toxic effects after maintenance treatment with rituximab.

The RCT by Salles et al. (7) found that rituximab maintenance therapy improves PFS in patients with follicular lymphoma who respond to a combination of chemotherapy plus rituximab administered as first-line treatment. To date, no benefit in OS has been reported and longer follow-up is needed to investigate the impact of rituximab maintenance therapy on OS.

New Reviews and Protocols in the Cochrane Library

In the latest issues of the Cochrane Library (Issue 6, 2010–Issue 2, 2011; see www.thecochranelibrary.com), two new reviews, one review update, and eight new protocols were published.

New Review 1: Deferasirox for Managing Iron Overload in People With Myelodysplastic Syndrome (23)

Clinical Background.

Myelodysplastic syndromes, a heterogeneous group of disorders, are characterized by myeloid and/or erythroid, and/or megakaryocytic dysplasia and is associated with ineffective hematopoiesis and a high rate (~70%) of transformation to acute myeloid leukemia. In the general population, myelodysplastic syndromes are rare with an incidence of approximately 5 cancers per 100 000 people. This rate increases with age (50 cancers per 100 000 people for those older than 70 years) (24). Because of symptomatic anemia, most patients require supportive therapy including repeated red blood cell transfusions, which cause the accumulation of iron (25). An iron overload is associated with the risk of organ dysfunction and reduced life expectancy (26). Iron chelation therapy is typically used to avoid an iron overload because the human body has no natural means of discarding it. The conclusion of Meerpohl et al. (23) is that it is unclear whether the new oral chelator deferasirox leads to a clinical benefit in patients with high iron levels.

Contribution.

Meerpohl et al. (23) searched different databases for RCTs examining deferasirox compared with no therapy, placebo, or another iron chelating treatment schedule. To date, the authors have identified only one ongoing study comparing deferasirox with deferoxamine for inclusion in their review; therefore, data are not currently available.

Implications for Practice.

Meerpohl et al. (23) conclude that recommendations about the consideration of iron chelation therapy for low-risk myelodysplastic syndromes cannot be supported by high-quality data from RCTs at this time. Therefore, data from the ongoing trial are urgently needed to warrant the widespread use of deferasirox outside clinical studies. However, in the interval, the decision to use deferasirox for individual patients should be on the basis of personal preferences considering potential benefits as well as harms.

New Review 2: Chemotherapy Alone vs Chemotherapy Plus Radiotherapy For Early-Stage Hodgkin Lymphoma (27)

Clinical Background.
HL is a malignancy of the lymphatic system that can occur in children and adults, but it is more common in the third decade of life. It is one of the most curable forms of cancer. Generally, the disease is differentiated into early-stage and advanced-stage HL. The review by Herbst et al. (27) focuses on the therapy options of early-stage HL. Although both chemotherapy alone and combined chemotherapy plus radiotherapy are effective for the treatment of early-stage HL, the optimal choice of treatment for these patients is discussed.

**Contribution.**

The review by Herbst et al. (27) includes 1245 patients from five trials in the main analysis and found that the addition of radiotherapy to six cycles of chemotherapy is a better treatment option than six cycles of the same chemotherapy alone in patients with early-stage HL. The meta-analysis showed statistically significantly increased to OS (HR = 0.40, 95% CI = 0.27 to 0.61); number needed to treat is 11 to 55 patients depending on risk of death and tumor control (HR = 0.41, 95% CI = 0.25 to 0.66); the number needed to treat is five patients. CR and ORR were similar among the two treatment arms. Both chemotherapy alone and combined modality treatment seem to be effective in the short term. Differences in outcomes between the two treatment arms emerged when patients were followed up for several years (the median follow-up period of the studies ranged between 22 months and 11 years). Furthermore, the rate of adverse events was also similar between the treatment arms, although only one trial reported secondary malignancies. Because adding radiotherapy may result in more secondary malignancies, or cardiac disease and deaths, long-term follow-up (>15 years) of clinical trials examining treatment options in early-stage HL should be performed.

Limitations of the review by Herbst et al. (27) include that inconsistencies among the five trials used for analysis may be caused by different chemotherapy regimens, but the summarized hazard ratios in the subgroup analyses by chemotherapy regimens were similar. Another potential limitation might be that the trials used different radiotherapy fields (involved field was used in three trials and extended field was used in two trials), but no difference in OS was observed between trials that examined the addition of involved-field or extended-field radiotherapy.

**Implications for Practice.**

The authors conclude that the currently available evidence suggests that patients should not avoid additional radiotherapy. Chemotherapy plus radiotherapy is superior to the identical chemotherapy administered alone in patients with early-stage HL in terms of rates of death and tumor relapse.

**New Protocols**

Cochrane reviews published eight new protocols.

**Protocol 1**

The first protocol by Martí-Carvajal et al. (28) entitled “Treatment for disseminated intravascular coagulation in patients with acute and chronic leukemia” assessed the clinical effectiveness and safety of pharmacological interventions such as heparins (low–molecular weight heparin and unfractionated heparin), danaparoid sodium, synthetic protease inhibitor with antithrombin, human recombinant activated protein C, recombinant human soluble thrombomodulin, recombinant tissue factor pathway inhibitor, recombinant activated factor VIIa, and recombinant hirudin with antifibrinolytic drugs for treating disseminated intravascular coagulation in patients with acute or chronic leukemia.

**Protocol 2**

The second protocol by Pidala et al. (29) entitled “Allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia (ALL) in first complete remission” provided evidence of the
affectivity of a sibling donor allocated to allogeneic hematopoietic cell transplantation compared with those without a sibling donor who were assigned to nonallogeneic hematopoietic cell transplantation therapy. The review will assess OS, PFS, relapse, treatment-related mortality, quality of life, and adverse events.

Protocol 3
The third protocol by Franklin et al. (30) entitled “Optimisation of chemotherapy and radiotherapy for untreated Hodgkin lymphoma patients with respect to second malignant neoplasms, overall and progression-free survival” compared the risks of secondary malignant neoplasms including secondary solid tumors, secondary NHL, and secondary AML in HL patients according to the design of first-line treatment, which includes use of chemotherapy, radiotherapy, or both, type and amount of chemotherapy, and the extent and dosage of radiation.

Protocol 4
The fourth protocol by Schlaak et al. (31) entitled “Allogeneic stem cell transplantation versus conventional therapy for advanced primary cutaneous T cell lymphoma” assessed OS, PFS, relapse, treatment-related mortality, quality of life, and adverse events after allogeneic stem cell transplantation compared with conventional therapy.

Protocol 5
The fifth protocol by Itchaki et al. (32) entitled “Anthracyclines-containing regimens for treatment of follicular lymphoma in adults” evaluated OS, PFS, CR, ORR, response duration, relapse, quality of life, and adverse events after anthracycline-containing regimens with or without radiotherapy compared with non-anthracycline-containing regimens.

Protocol 6
The sixth protocol by Ossendorf et al. (33), “Idiotype vaccination for Non-Hodgkin lymphoma” evaluated the therapeutic benefit of idiotype vaccination compared with no further treatment by measuring OS, PFS, response rate, treatment-related mortality, adverse events, and quality of life.

Protocol 7
The seventh protocol by Zeng et al. (34) entitled “Pegylated liposomal doxorubicin for multiple myeloma” assessed the effectiveness of pegylated liposomal doxorubicin vs placebo, no treatment, or another active agent with respect to OS, PFS, time to progression, very good partial response, adverse events, and quality of life.

Protocol 8
The eighth protocol by Wheatley et al. (35) entitled “Thalidomide, lenalidomide and their analogues, as therapy for multiple myeloma” evaluated thalidomide and other immunomodulatory drugs compared with placebo or no treatment, or other active treatment with respect to OS, PFS, time to progression, CR, partial response, adverse events, and quality of life.

References


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