Fourteenth Biannual Report of the Cochrane Haematological Malignancies Group—Focus on Autologous Stem Cell Transplantation in Hematological Malignancies

Michaela Rancea, Nicole Skoetz, Ina Monsef, Kai Hübel, Andreas Engert, Kathrin Bauer

Affiliations of authors: Cochrane Haematological Malignancies Group (MR, NS, IM, AE, KB), Department of Internal Medicine (KH, AE), University Hospital of Cologne, Cologne, Germany.

Correspondence to: Michaela Rancea, Cochrane Haematological Malignancies Group (CHMG), Department of Internal Medicine, University Hospital of Cologne, Kerpener Street 62, 50924 Cologne, Germany (e-mail: michaela.rancea@uk-koeln.de).

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This 14th biannual report of the Cochrane Haematological Malignancies Group (CHMG) highlights recently published randomized controlled trials (RCTs) in the field of hemato-oncology, covering the publication period from March 2011 to October 2011. Implications for clinical practice and methodological aspects are the main principles for selecting trials for this report. Studies were identified by 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 October 25, 2011. In this present summary of key features of recent RCTs, we focus on autologous stem cell transplantation (ASCT). Of the 65 identified RCTs, 3 trials that evaluated different aspects of ASCT in hematologic malignant patients are presented in detail [1–3]. Six further trials of high clinical importance are presented in short version [4–9].

After a short overview of the clinical relevance and the selection of patients for the trials, we discuss important methodological aspects of each trial (eg, 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 the trials in focus. In addition, we outline the latest Cochrane Reviews [10–15] and protocols [16–29] published by the CHMG.

Published Trials in Patients Who Underwent ASCT

Clinical Background: ASCT

ASCT is a procedure commonly used in patients with lymphoma and multiple myeloma and less often in leukemia and in the treatment of solid tumors. The aim of ASCT is to restore the bone marrow in patients with severe or complete depletion of bone marrow cells caused by myeloablative high-dose chemotherapy [30]. ASCT means that patients receive stem cells from their own blood. After induction chemotherapy, stem cells are mobilized and harvested, followed by the application of high-dose chemotherapy. ASCT leads to a rapid (8–12 days) recovery of the immune function, which might protect the patients against severe infections. In relapsed Hodgkin lymphoma (HL) patients, for example, ASCT has even achieved an improvement in progression-free survival and has, therefore, evolved to standard therapy after high-dose chemotherapy [29,31]. There are several hematological malignances including HL, non-Hodgkin lymphoma (NHL), acute myeloid leukemia (AML), and chronic lymphocytic leukemia (CLL) where
ASCT might be indicated. Below we discuss currently published trials that examined the efficacy and safety of ASCT in different hematological diseases.

**Trial 1: Hematopoietic ASCT in CLL Patients Who Are in CR**


**Clinical Background.**

CLL accounts for 25% of all leukemias and is the most common lymphoid malignancy in Western countries. The disease is characterized by a highly variable clinical course and prognosis. A proportion of 40% is younger than 65 years at time of diagnosis, and these younger patients might die from their disease. Only allogeneic stem cell transplantation provides a potential for cure. Unfortunately, the efficacy of this treatment option is limited by the availability of donors as well as its high proportion of nonrelapsed deaths. Therefore, alternative treatment approaches are needed that improve time to next treatment and overall survival (OS). Michallet et al. [1] evaluated the efficacy of autologous stem cell transplantation compared with no further treatment for responding CLL patients after first- or second-line treatment.

**Contribution.**

This trial enrolled adult patients, range 31–65 years of age, with CLL in complete remission (CR) after first- or second-line treatment who were randomly assigned to receive either ASCT arm (n = 112) or no additional treatment (observation arm, n = 111) (Table 1). The trial included 223 patients instead of the calculated 270 participants because of slow accrual. Patients received different induction regimens (investigators’ choice). Only 4% of these regimens included rituximab. Subsequently, all patients received mobilization treatment consisting of cyclophosphamide, 2-mercaptoethane sulfonate sodium and subcutaneous lenograstim or, alternatively, a Dexa-BEAM regimen (dexamethasone, carmustine, etoposide, cytarabine, lenograstim). Only 80 patients (72%) of 112 assigned to the autografting arm actually underwent transplantation. After a median follow-up of 43.7 months, there was no statistically significant difference in nonrelapse mortality between the two study arms (4% ASCT arm vs 0% observation arm, \( P = .33 \)), but the autografting resulted in a statistically significantly improved event-free survival (EFS) (hazard ratio [HR] = 0.44, 95% confidence interval [CI] = 0.30 to 0.65, \( P < .001 \)) and time to disease requiring therapy or death (HR = 0.39, 95% CI = 0.26 to 0.59, \( P < .001 \)). These results did not translate into a statistically significant improvement of OS (HR not provided, \( P = .77 \)). Unfortunately, the trial does not provide any safety analyses, except for the occurrence of myelodysplastic syndrome (MDS) (three patients in the ASCT arm vs one patient in the observation arm).

**Implication for Practice.**

This trial showed that CLL patients in CR after chemotherapy benefit from the administration of ASCT in EFS and time to disease requiring therapy without a statistically significant difference of nonrelapse mortality. There was no statistically significant difference in OS. It remains unclear which adverse events (AEs) have to be expected by the patients, and further trials are needed to evaluate this approach in the era of induction therapy with rituximab.

**Most Interesting Feature.**

This trial assessed the feasibility and efficacy of ASCT for CLL patients in CR. A proportion of 72% allocated to the ASCT arm finally received the transplant, and the trial showed a statistically significant improvement in EFS but not for OS. However, the early closure of the trial because of slow recruitment (only 76% of the initially estimated sample size was included) might have introduced bias.
<table>
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<th><strong>Feature</strong></th>
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| **Sample size calculation** | 134 in each arm, stated target accrual was 270 patients, on the basis of 5-year EFS to detect an absolute increase of 20% with a power of 90%  
Trial Management Group closed the trial before target accrual was met (n = 223 patients) because of slow accrual     |
| **Randomization**   | Generation of allocation sequences was not reported  
Concealment of allocation was by telephone or fax                                                                                                                                                           |
| **Blinding**        | Open-label                                                                                                                                                                                                |
| **Setting**         | 11 different European countries (France, United Kingdom, Germany, Switzerland, amongst other unnamed European countries)  
≥18 years of age  
Confirmed CLL diagnosis  
Progressive Binet stage A, B, or C                                                                                                                                                                    |
| **Patients**        | Patients in CR, nodular partial remission, very good partial remission after first- or second-line treatment  
No patients with poor performance status (WHO grade >2) or severe morbidities of kidney, liver, heart or with neurological or psychological diseases  
Trial did not test induction therapy (decision for first- and second-line treatment was made by the investigators)  
Administred regimens contained fludarabine and alkylating agents (concurrently or sequentially) in 71% of patients; only 9 patients (4%) received combinations of purine analogues and rituximab.  
Recommended mobilization schedule for all patients (n = 223): 2 g/m² cyclophosphamide at day 1 with 2-mercaptoethane sulfonate sodium intravenously and 150 μg/m²/day lenograstim (days 5–12) subcutaneously; peripheral blood cell collection for all patients were performed on 2–4 consecutive days after hematopoietic recovery phase  
Alternative mobilization schedule for autografting arm: Dexa-BEAM: 3 × 8 mg dexamethasone (days 1–10), 60 mg/m² carmustine (day 2), 75 mg/m² etoposide (days 4–7), 100 mg/m² cytarabine every 12 h (days 4–7), 20 mg/m² melphalan (day 3) all given intravenously, and 150 μg/m² lenograstim (day 11) subcutaneously until the last day of aphaeresis  
Conditioning regimen in case of failure of mobilization (two alternatives):  
(1) 60 mg/kg body weight cyclophosphamide (days -5 to -4) with 2-mercaptoethane sulfonate sodium plus 10 Gy total body irradiation (days -3 to -1)  
(2) BEAM: 300 mg/m² carmustine (day -6), 200 mg/m² cytarabine (every 12 h on days -5 to -2), 100 mg/m² etoposide (days -5 to -2), 140 mg/m² melphalan (day -1), all given intravenously  
Additional therapy: Granulocyte-colony stimulating factors after transplantation  
No. of patients randomly assigned to treatment arms: 223 patients (1:1), 112 patients allocated to ASCT, 111 patients allocated to observational arm  
No. of discontinuations: 72 patients (80%) in ASCT arm actually underwent transplantation (reasons for failures included 22 collection failures, 5 patient refusals, 2 progressive diseases or secondary malignancy, and 2 postinduction complications) |
| **Study drug regimen** | Dexa-BEAM: 3 × 8 mg dexamethasone (days 1–10), 60 mg/m² carmustine (day 2), 75 mg/m² etoposide (days 4–7), 100 mg/m² cytarabine every 12 h (days 4–7), 20 mg/m² melphalan (day 3) all given intravenously, and 150 μg/m² lenograstim (day 11) subcutaneously until the last day of aphaeresis  
Conditioning regimen in case of failure of mobilization (two alternatives):  
(1) 60 mg/kg body weight cyclophosphamide (days -5 to -4) with 2-mercaptoethane sulfonate sodium plus 10 Gy total body irradiation (days -3 to -1)  
(2) BEAM: 300 mg/m² carmustine (day -6), 200 mg/m² cytarabine (every 12 h on days -5 to -2), 100 mg/m² etoposide (days -5 to -2), 140 mg/m² melphalan (day -1), all given intravenously  
Additional therapy: Granulocyte-colony stimulating factors after transplantation  
No. of patients randomly assigned to treatment arms: 223 patients (1:1), 112 patients allocated to ASCT, 111 patients allocated to observational arm  
No. of discontinuations: 72 patients (80%) in ASCT arm actually underwent transplantation (reasons for failures included 22 collection failures, 5 patient refusals, 2 progressive diseases or secondary malignancy, and 2 postinduction complications) |
| **Patient flow**    | Median follow-up = 43.7 mo  
Sample size calculation was on the basis of an intention-to-treat analysis, but the article did not provide further information on the actual No. of patients included in the survival, mortality, and AEs analyses  
Primary outcome was EFS  
Secondary outcomes included OS, time to disease requiring therapy or death, mortality after transplantation  
Analyses of AEs were not planned |
Results

EFS: HR = 0.44, 95% CI = 0.30 to 0.65, \( P < .001 \); EFS at 5 years = 42% ASCT arm vs 24% observation arm; median EFS = 51 mo ASCT arm vs 24 mo observation arm.

OS: after a median follow-up of 43.7 mo, similar OS for both arms (HR not provided, \( P = .77 \)); OS at 5 years = 85.5% ASCT arm vs 84.3% observation arm.

Time to disease requiring therapy or death: HR = 0.39, 95% CI = 0.26 to 0.59, \( P < .001 \). Relapse incidence at 5 years for ASCT vs observation = 54.2% vs 75.5%, respectively. Median time to relapse = 65 mo for ASCT arm vs 40 mo for observation arm, \( P = .002 \).

Nonrelapse mortality: Nonrelapse mortality was similar between the two study arms (ASCT vs observation arm = 4% vs 0%, \( P = .03 \)).

Additionally reported: Only incidence of myelodysplastic syndromes provided were for 3 ASCT patients and 1 observation patient.

Potential conflict of interest

All authors declared no competing financial interests.

*ASCT = autologous stem cell transplant; CI = confidence interval; CLL = chronic lymphocytic leukemia; EFS = event-free survival; HR = hazard ratio; OS = overall survival; WHO = World Health Organization.

**Trial 2: Hematopoietic ASCT for CLL Patients Who Are Not in CR**


Clinical Background.

As stated earlier, alternative treatment approaches are needed to improve the time to next treatment as well as OS for patients with CLL. Sutton et al. [2] reported the results of a RCT evaluating ASCT administrated after induction chemotherapy. Patients who achieved CR were randomly assigned to the European intergroup trial published by Michallet et al. [1], discussed above. Therefore, we restricted this discussion on the presented results of patients who did not achieve CR.

Contribution.

This group of patients, who did not achieve CR after induction therapy with mini-doxorubicin, vincristine, cyclophosphamide, prednisone (referred to as mini-CHOP) plus fludarabine, was randomly assigned to receive either ASCT (n = 46) or fludarabine plus cyclophosphamide (n = 48). After a median follow-up of 51.2 months, EFS rates at 3 years (48.9% for ASCT arm vs 44.4% for fludarabine plus cyclophosphamide arm, \( P = .69 \)) and OS (HR = 1.21, 95% CI = 0.49 to 2.99, \( P = .68 \)) were similar between both arms. In addition, the rates of grade 3 or 4 AEs, particularly in treatment-related deaths (6% ASCT arm vs 4% fludarabine plus cyclophosphamide arm, \( P = .61 \)), bacterial infections or aplasia (9% ASCT arm vs 7%fludarabine plus cyclophosphamide arm, \( P = .95 \)), were similar. No differences in long-term toxicities, such as MDS or AML (3% ASCT arm vs 2% fludarabine plus cyclophosphamide arm, \( P = .54 \)) or solid tumors (3% ASCT arm vs 4% fludarabine plus cyclophosphamide arm, \( P = .59 \)), were observed (Table 2).

Implication for Practice.

The trial included 94 instead of 128 patients but did not explain why it excluded some patients. ASCT was administered to 74% of the patients allocated to this treatment arm. The trial did not show beneficial effects of ASCT compared with fludarabine plus cyclophosphamide in EFS, CR,
or OS for patients not achieving CR after induction treatment nor did it indicate statistically significant differences in the occurrence of severe AEs.

**Most Interesting Feature.**
The trial evaluated the feasibility of ASCT for CLL patients not achieving CR but failed to show improvement of efficacy.

**Table 2. Key features of Sutton et al.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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<tbody>
<tr>
<td>Sample size calculation</td>
<td>Sample size for the non-CR group: 64 patients per arm were required to predict a 20% benefit of 3-year EFS in the FC arm and a 30% benefit of ASCT. Only 94 instead of 128 patients were recruited (the trial provided no comment for the smaller sample size).</td>
</tr>
<tr>
<td>Randomization</td>
<td>Generation of allocation sequences was done with permutation blocks. Concealment of allocation by centralized phone procedure.</td>
</tr>
<tr>
<td>Blinding</td>
<td>Open-label.</td>
</tr>
<tr>
<td>Setting</td>
<td>37 centers in France and Belgium.</td>
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<tr>
<td>Patients</td>
<td>Included those who were 18-65 years of age with Binet stage B or C CLL and who were previously untreated.</td>
</tr>
<tr>
<td>Study drug</td>
<td>Upfront treatment for all patients included: 3 cycles mini-CHOP: 25 mg/m² doxorubicin, 1 mg/m² vincristine (day 1), both given intravenously, 300 mg/m²/d cyclophosphamide (days 1–5), 40 mg/m²/d prednisone (days 1–5), both administrated orally, followed by 3 cycles 25 mg/m²/d fludarabine intravenously or 40 mg/m²/d fludarabine (days 1–5) orally. The authors stated that patients in CR after the upfront treatment were randomly assigned to the RCT run by Michallet et al. Patients not in CR were randomly assigned to treatment as follows: all patients not in CR received 1 or 2 cycles DHAP: 100 mg/m² cisplatinum (24 h continuously on day 1), 2000 mg/m² cytarabine (3 h twice on day 2), 40 mg/d dexamethasone (days 1–4), all given intravenously. Patients were then subsequently randomized: Interventional arm: conditioning and mobilization ASCT, 60 mg/m²/d cyclophosphamide (day 2) intravenously, fractionated total body irradiation 10 Gy with lung protection above 8 Gy (during 3 days), and 150 µg/m²/d lenograstim (day after DHAP until last day of autologous stem cell collection). Control arm: chemotherapy alone (FC arm), 3 monthly courses of 25 mg/m²/d fludarabine and 300 mg/m²/d cyclophosphamide, both given intravenously on days 1–3. Additional treatment included a second mobilization procedure if necessary, hematopoietic growth factors only for mobilization, and prevention of viral pneumonia with trimethprim, sulfamethoxazole, and acyclovir for 6 mo or longer after treatments.</td>
</tr>
<tr>
<td>Patient flow</td>
<td>94 patients were randomly assigned to the non-CR group, 46 to ASCT, and 48 patients to FC. Discontinuation of patients not in CR: 12 of 46 patients in ASCT arm (7 mobilization failure, 1 death, 2 progression, and 1 patient refusal) and 8 of 48 patients in FC arm (1 ASCT, 4 patient refusal, and 3 unknown).</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>Median follow-up after patients were randomly assigned to treatment arms who were not in CR was 51.2 mo.</td>
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</table>
Trial 3: Autologous Hematopoietic Stem Cell Transplantation in Newly Diagnosed AML Patients Achieving CR


Clinical Background.

AML is a malignant disease of the hematopoietic stem cells. Up to 50% of the patients are younger than 60 years of age at the time of diagnosis. The patient’s age plays a critical role for this disease. Treatment approaches differentiate between patients younger than 60 years or 60 years and older. Although approximately 80% of adult AML patients younger than 60 years reach a CR, most will relapse if they do not receive further consolidation treatment. Therefore, the recommended therapy for adult patients in CR age 60 years or younger is high-intensive chemotherapy with or without allogeneic stem cell transplantation. Investigated alternatives for young adults in CR without a HLA-matched donor are ASCT, further intensive postremission chemotherapy, or no further therapy. Vellenga et al. [3] analyzed the efficacy of ASCT compared with intensive chemotherapy in young adult AML patients achieving CR without an eligible donor (Table 3).

Contribution.

This randomized multicenter study included young adult, newly diagnosed AML patients between 16 and 60 years of age, with favorable, intermediate, unfavorable, or very unfavorable cytogenetic risk from two randomized trials (AML-29 and AML-42) [32,33]. After induction

<table>
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<th>Feature</th>
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<tbody>
<tr>
<td>Analysis</td>
<td>Intention-to-treat principle</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome: EFS</td>
</tr>
<tr>
<td></td>
<td>Secondary outcomes: OS, CR, stem cell mobilization, and AEs</td>
</tr>
<tr>
<td>Results</td>
<td>EFS (non-CR group): HR and P not provided; EFS rate at 3 years = 48.9% in ASCT arm vs 44.4% in FC arm, P = .55</td>
</tr>
<tr>
<td></td>
<td>OS (non-CR group): Similar between both arms; HR = 1.21, 95% CI = 0.49 to 2.99, P = .68; survival rate at 3 years = 81.7% in ASCT arm vs 87.0% in FC arm, P = .69</td>
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<td></td>
<td>Complete response: 27 of 46 patients (58.7%) in the ASCT arm and 26 of 48 patients (54.2%) in the FC arm</td>
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<td></td>
<td>Stem cell mobilization: 34 of 46 patients (74%) actually received ASCT in the non-CR group</td>
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<td>AE (WHO grade 3 to 4, P values were not provided): Hemolytic anemia = 0% in ASCT arm vs 2% in FC arm; bacterial infections/aplasia = 9% in ASCT arm vs 7% in FC arm; richter lymphoma = 6% in ASCT arm vs 2% in FC arm; myeloma = 0% in ASCT arm vs 2% in FC arm; MDS/AML = 3% in ASCT arm vs 2% in FC arm; solid tumor = 3% in ASCT arm vs 4% in FC arm; treatment-related deaths = 6% in ASCT arm vs 4% in FC arm</td>
</tr>
<tr>
<td>Potential conflict of interest</td>
<td>All authors declared no competing financial interests</td>
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</tbody>
</table>

Funding was from the French Ministry of Health and Foundation, Georgelin and Chugai Pharma, France

*AE = adverse event; ASCT = autologous stem cell transplant; CI = confidence interval; CR = complete response; EFS = event-free survival; FC = fludarabine plus cyclophosphamide; HR = hazard ratio; MDS/AML = myelodysplastic syndrome/acute myeloid leukemia; OS = overall survival; RFS = relapse-free survival; WHO = World Health Organization.
within these trials, patients in CR without an HLA-matched donor were allocated to receive either busulfan plus cyclophosphamide with ASCT (n = 258) or intensive chemotherapy alone with etoposide and mitoxantrone (n = 259). After a median follow-up of 106 months, patients in the ASCT arm had statistically significantly fewer relapses at 5 years (58% ASCT arm vs 70% chemotherapy arm, \( P = .02 \)). However, the statistically significant effect on relapse at 5 years did not lead to statistically significant differences in OS (HR not provided, \( P = .86 \)) or relapse-free survival (HR = 0.82, 95% CI = 0.66 to 1.1, \( P = .07 \)). The nonrelapse mortality rate at 5 years was statistically significantly increased within the ASCT group (4% ASCT arm vs 1% chemotherapy alone arm, \( P = .02 \)). Initially, the treatment with ASCT led to statistically significantly higher neutrophil recovery rates (\( P < .001 \)), but the incidence rates of bleedings (WHO grade 3 to 4 = 3% ASCT arm vs 2% chemotherapy alone arm) or infections (WHO grade 3 to 4 = 46% ASCT arm vs 44% chemotherapy alone arm) were similar between the two treatment arms.

**Implication for Practice.**
Young adult AML patients in CR who received ASCT experienced a lower relapse rate at 5 years although statistically significant improvements in OS or relapse-free survival were not observed. Moreover, treatment with ASCT caused more statistically significant nonrelapse deaths at 5 years. Initially after treatment, the neutrophil recovery rates were improved by additional ASCT treatment compared with chemotherapy alone and were not associated with statistical differences in the occurrence of severe infections or bleedings.

**Most Interesting Feature.**
This was a large randomized trial assessing the effects of ASCT in newly diagnosed young adult AML patients in CR (n = 517) who were not eligible for allogeneic transplantation. In total, 91% of the patients assigned to ASCT actually received ASCT. However, it failed to show improved relapse-free survival or OS.

**Table 3.** Key features of Vellenga et al. [3]*

<table>
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<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>Sample size calculation</td>
<td>No information on sample size provided. After a follow-up of 3.5 years, 343 events were observed in both groups (relapse or death in CR). This number of events gives a power of 71% for the detection of an increase in the 5-year RFS from 30% in the chemotherapy arm to 50% in the ASCT arm</td>
</tr>
<tr>
<td>Randomization</td>
<td>Generation of allocation sequences: biased-coin minimization procedure</td>
</tr>
<tr>
<td>Blinding</td>
<td>Open label</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicenter study (no further information provided)</td>
</tr>
<tr>
<td>Patients</td>
<td>Patients from the AML-29 and AML-42 [32,33] were included and randomly assigned to treatment arms in this trial</td>
</tr>
<tr>
<td>Previously untreated: 16–60 years of age from AML-29 trial</td>
<td></td>
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<tr>
<td>Previously untreated: 18–60 years of age from AML-42 trial</td>
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<tr>
<td>Patients in CR with standard-risk or unfavorable-risk AML patients not eligible for allogeneic stem cell transplant</td>
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</tr>
<tr>
<td>Study drug</td>
<td>Induction therapy (AML-29 and AML-42 patients): 1 cycle of cytarabine 200 mg/m² (days 1–7) plus 12 mg/m² idarubicin (days 6–8), 1 cycle of 1000 mg/m² cytarabine every 12 h (days 1–6) plus 120 mg/m²amsacrin (days 4–6)</td>
</tr>
<tr>
<td>AML-42: Patients randomly assigned to 1000 mg/m² cytarabine (days 1–5) or 2000 mg/m² twice daily (days 1, 2, 4, 6)</td>
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<tr>
<td>AML-29 (and part of AML-42 patients): G-CSF vs no G-CSF during</td>
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cycles 1 and 2
Randomized consolidation therapy:
Interventional arm = 4 mg/kg busulfan (days -4 through -7), 60 mg/kg cyclophosphamide (days -2 to -3) followed by ASCT
Control arm = 1 cycle chemotherapy consisting of 100 mg/m² etoposide (no further information provided) and 10 mg/m² mitoxantrone (no further information provided)
Additional therapy: No further recommendations were provided

Patient flow
The No. of patients randomly assigned to treatment arms: 2017 patients enrolled for remission induction and 1534 (76%) of these achieved first CR; only 517 patients matched the inclusion criteria for random assignment to ASCT or chemotherapy
No. of patients analyzed = 517; 258 patients in ASCT arm and 259 patients in chemotherapy alone arm
No. of discontinuations: 5 patients in chemotherapy arm and 7 in ASCT arm were excluded because of ineligibility (6 had acute promyelocytic leukemia, 2 never reached CR, 2 relapsed before random assignment, and 2 had an incorrect diagnosis)

Duration of follow-up
Median follow-up = 106 mo

Analysis
Intention-to-treat principle

Outcomes
Primary outcome: RFS (defined as interval between random assignment and the date of death or the date of relapse)
Secondary outcomes: OS, relapse rate at 5 years, time to hematopoietic recovery, and AEs

Results
RFS: No statistically significant difference (HR = 0.82, 95% CI = 0.66 to 1.1, \( P = .06 \)); RFS rate at 5 years = 38% in ASCT arm vs 29% in chemotherapy alone arm
OS: No statistically significant difference (HR not provided, \( P = .86 \)); OS rate at 5 years = 44% ASCT arm vs 41% chemotherapy alone arm
Relapse rate at 5 years: 58% ASCT arm vs 70% chemotherapy alone arm, \( P = .02 \)
Hematopoietic recovery: neutrophil counts > 0.5 × 10⁹/L at day 14 = 32% ASCT arm vs 1% chemotherapy alone arm, \( P < .001 \)
Neutrophil counts > 0.5 × 10⁹/L at day 28 = 88% ASCT arm vs 43% in chemotherapy alone arm, \( P < .001 \)
AEs (WHO grade 3 to 4): bleeding = 3% ASCT arm vs 2% chemotherapy alone arm; infection = 46% in ASCT arm vs 44% in chemotherapy alone arm; nonrelapse mortality at 5 years = 4% ASCT arm vs 1% chemotherapy alone arm, \( P = .02 \)

Potential conflict of interest
All authors declared no potential conflicts of interest

*AE = adverse event; AML = acute myeloid leukemia; ASCT = autologous stem cell transplant; CI = confidence interval; CR = complete response; G-CSF = granulocyte colony-stimulating factor; HR = hazard ratio; RFS = relapse-free survival

**Other Interesting Trials**

**Trial 4: Chronic graft-vs-host disease: long-term results from a randomized trial on graft-vs-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius**
Graft-vs-host disease (GvHD) is a common complication after allogeneic stem cell transplantation, caused by the recognition of host antigens as foreign by donor T lymphocytes. GvHD increases non-transplantation mortality as well as morbidity caused by the immune reaction against the host’s body cells. GvHD is categorized as acute (occurrence within the first 100 days after stem cell transplantation) and chronic (occurrence after this 100-day interval). Antithymocyte globulins (ATGs) are IgG antibodies (from the serum of rabbits or horses) against the human T cells. This randomized, open-label, multi-center trial assessed prophylactic treatment of GvHD with ATGs in addition to cyclosporine and methotrexate (n = 103) compared with cyclosporine and methotrexate alone (n = 98) in adult patients with hematopoietic cell transplantation from an unrelated donor. Both prophylactic regimens were administered before transplantation. First results of this trial were published by Fink et al. [34], who presented long-term results after a median follow-up of 3 years—specifically the occurrence of chronic GvHD. The additional administration of ATGs statistically significantly reduced the cumulative incidence of extensive chronic GvHD (HR = 0.20, 95% CI = 0.1 to 0.39, \( P < .0001 \)) and the cumulative incidence of limited and extensive chronic GvHD (HR = 0.34, 95% CI = 0.21 to 0.55, \( P < .0001 \)). This did not lead to statistically significant differences in OS (HR = 0.84, 95% CI = 0.56 to 1.25, \( P = .39 \)), disease-free survival (DFS; HR = 0.93, 95% CI = 0.64 to 1.36, \( P = .71 \)), or the incidence of relapses (HR = 1.21, 95% CI = 0.72 to 2.02, \( P = .47 \)). The cumulative incidence of late bacterial infections (HR = 0.68, 95% CI = 0.39 to 1.17, \( P = .16 \)) and the incidence of nonrelapse-related mortality (HR = 0.68, 95% CI = 0.38 to 1.20, \( P = .18 \)) were also similar between the two treatment arms.

Implication for Practice.
This RCT showed that additional ATG caused statistically significant decrease in incidences of extensive and limited chronic GvHD compared with standard GvHD prophylaxis with cyclosporine and methotrexate alone. This did not lead to statistically significant differences in OS, DFS, late bacterial infections, or the incidence of relapses between both arms. There was also no difference in the nonrelapse-related mortality.

Trial 5: Autologous transplantation gives encouraging results for young adults with favorable-risk acute myeloid leukemia but is not improved with gemtuzumabozogamicin

As stated earlier (see trial 3), the main challenge in young adults with AML is the prevention of relapses. One promising option might be the administration of targeted therapy with monoclonal antibodies to deepen the quality of remission. Gemtuzumabozogamicin (GO) is an anti-CD33 monoclonal antibody that was initially approved for the treatment of older adults with AML in first relapse. Fernandez et al. [6] evaluated the efficacy and safety of GO in consolidation treatment of younger AML patients (between 17 and 60 years of age) in CR before administration of ASCT.

In total, 270 patients were allocated to ASCT and randomly assigned to treatment arms (138 in the GO arm and 132 in the control arm). Of these, only 138 patients (72 in the GO arm, 66 in the control arm) received ASCT. The most important reasons of not proceeding to ASCT included disease progression, inadequate stem cell collection, and patient refusal. The induction therapy for all patients consisted of daunorubicin (45 mg/m²/day for 3 days or 90 mg/m²/day for 3 days) plus cytarabine (100 mg/m²/day for 7 days). All patients in CR allocated to ASCT received consolidation treatment with high-dose cytarabine therapy (3 g/m² given intravenously
over a 3-h period every 12 h, every other day for a total of six doses) followed by 250 μg/m² sargramostim until blood counts returned to baseline levels. After stem cell collection, patients randomly assigned to the investigational arm received a single dose of GO (6 mg/m²) followed by 250 μg/m² sargramostim until blood cell counts returned to baseline levels. An intention-to-treat analysis was performed for all 270 randomly assigned patients. After a median follow-up of 50.9 months, there was no statistically significant difference in OS (HR = 1.11, 95% CI = 0.81 to 1.53, P = .52; median OS = 27.9 months GO arm vs 35.5 months no GO arm), DFS (HR = 1.10, 95% CI = 0.82 to 1.48, P = .54; median DFS = 13.6 months GO arm vs 15.0 months no GO arm), or relapse incidence (P = .99). Furthermore, patients in the control arm had a more rapid recovery of neutrophils (87.9% GO arm vs 95.5% no GO arm, P = .06) and platelets (36.4% GO arm vs 60.6% no GO arm, P = .008). In addition, six patients treated with GO but no patients within the control arm developed veno-occlusive disease/sinusoidal obstruction syndrome after ASCT (no further data on safety was provided).

Implication for Practice.
This RCT showed that additional administration of the anti-CD33 monoclonal antibody GO during consolidation therapy before ASCT does not statistically significantly improve DFS or OS in younger AML patients in CR.

Trial 6: Eight cycles of BEACOPP escalated compared with 4 cycles of BEACOPP escalated followed by 4 cycles of BEACOPP baseline with or without radiotherapy in patients in advanced stage Hodgkin lymphoma (HL): final analysis of the HD12 trial of the German Hodgkin Study Group

HL is one of the most common malignancies in young adults and has become curable for the majority of patients even when their disease is in the advanced stage. For the treatment of advanced stages, the German Hodgkin Study Group (GHSG) developed the BEACOPP baseline (baseline dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen, which was later intensified by a shorter time (shorter cycle) and increased dose (increased single dose) called BEACOPP escalated. The most important challenge in treating HL is to find the optimal treatment with the highest efficacy and least toxic effects. Therefore, the HD12 study of the GHSG assessed two comparisons: 1) eight cycles of BEACOPP escalated were compared with the less intensive schedule of four cycles of BEACOPP escalated plus four cycles of BEACOPP baseline (chemotherapy comparison); and 2) administration of consolidating radiotherapy (RT) compared with no RT in patients who responded to chemotherapy and had initial bulky disease (>5 cm) or residual disease consisting of a tumor diameter of least 1.5 cm (RT comparison).

The multicenter trial included 1670 newly diagnosed patients, between 16 and 65 years of age, with advanced stage of HL. They were randomly assigned to one of four treatment groups: group 1 received eight cycles of BEACOPP escalated followed by 30 Gy RT (n = 421); group 2 received four cycles BEACOPP escalated and four cycles BEACOPP baseline (4 + 4) followed by 30 Gy RT (n = 422); group 3 received eight cycles BEACOPP escalated without RT (n = 415); and group 4 received 4 + 4 without RT (n = 412). After a median follow-up of 78 months, the comparison of both chemotherapy regimens showed no statistically significant difference in freedom from treatment failure (HR = 1.07; 95% CI = 0.83 to 1.38) and OS (HR = 1.14, 95% CI = 0.83 to 1.56). Eight cycles of BEACOPP escalated caused more anemia (65% BEACOPP...
escalated arm vs 50% 4 + 4 arm, P not provided), thrombocytopenia (66% BEACOPP escalated arm vs 51% 4 + 4 arm, P not provided) and secondary malignancies (5.5% BEACOPP escalated arm vs 4.2% 4 + 4 arm, P not provided). Interestingly, the 4 + 4 regimen was associated with a higher rate of death related to acute toxic effects of chemotherapy (2.4% BEACOPP escalated arm vs 3.4% 4 + 4 arm, P not provided), more progressive diseases (1.9% BEACOPP escalated arm vs 3.7% 4 + 4 arm, P not provided), and more relapses (4.8% BEACOPP escalated arm vs 5.2% 4 + 4 arm, P not provided).

When additional RT and no RT were compared, statistically significant differences were not observed for OS (HR = 1.09, 95% CI = 0.74 to 1.60) or freedom from treatment failure (HR = 1.29, 95% CI = 0.97 to 1.73). RT was well tolerated with only 3 grade-4 toxicities occurring among 575 patients who received RT. More secondary malignancies occurred in the RT arm vs the no RT arm (5.8% vs 4.2%, respectively, P not reported), whereas no RT led to more progressive diseases (2% vs 2.6%, respectively, P not reported) and relapses (4% vs 6.4%, respectively, P not reported).

**Implication for Practice.**

This well-designed and performed trial in patients with advanced stage HL could not demonstrate decreased toxic effects by reduction of chemotherapeutic intensity of treatment from eight cycles BEACOPP escalated to four cycles BEACOPP escalated plus four cycles BEACOPP baseline. Furthermore, the comparison between additional RT and no RT showed that OS and freedom from treatment failure were similar among the two groups.

**Trial 7: ABVD vs BEACOPP for Hodgkin’s lymphoma when high-dose salvage is planned**


Beside the already described BEACOPP escalated regimen initiated by the GHSG, there is another widely used standard chemotherapy for patients with advanced HL, the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine), which is well tolerated and easy to administer. The trial by Viviani et al. [9] compared the efficacy and safety of both regimens. It included 331 previously untreated HL patients with stadium IIB, III, and IV between 17 and 60 years of age who were randomly assigned to treatment with six up to eight cycles ABVD (n = 168) or to the regimen of four cycles BEACOPP escalated plus four cycles BEACOPP baseline (n = 163). In addition, patients received RT, in the case of partial response or residual disease, and salvage therapy, if they did not achieve CR or had a relapse. Different types of salvage regimens were used, because salvage therapy was recommended but not mandated.

After a median follow-up of 61 months, patients randomly assigned to the BEACOPP arm showed more complete responses (81% BEACOPP arm vs 76% ABVD arm, P value not provided), less relapses (4% BEACOPP arm vs 11% ABVD arm, P value not provided), and a statistically significantly improved freedom from first progression (HR = 0.46, 95% CI not provided, P = .004), which was the primary endpoint of the study. Moreover, there was a similar difference of 6 percentage points of the EFS rate at 7 years favoring BEACOPP (88% BEACOPP arm vs 82% ABVD arm, P = .12) and a statistically nonsignificant difference of 5 percentage points of the OS rate at 7 years favoring BEACOPP (89% BEACOPP arm vs 84% ABVD arm, P = .39). On the other hand, the treatment with BEACOPP caused statistically significantly more hematologic AEs (WHO grade 3 to 4, 81% BEACOPP arm vs 43% ABVD arm, P < .001) and nonhematologic AEs (19% BEACOPP arm vs 7% ABVD arm, P = .001).
Implication for Practice.
This relatively small trial demonstrated that patients treated with BEACOPP compared with ABVD showed more acute toxic effects but also benefit from treatment with BEACOPP in terms of more CRs, less relapses, and an overall improved FFFP. The administration of BEACOPP does not lead to a statistically significant improvement in EFS and OS.

Trial 8: Fludarabine plus alemtuzumab vs fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial

The administration of monoclonal antibodies in addition to standard chemotherapeutics has become a very promising approach for developing new treatment strategies to improve the clinical outcome of symptomatic patients. Elter et al. [5] assessed the efficacy and safety of fludarabine with or without the additional administration of the anti-CD52 monoclonal antibody alemtuzumab in patients with relapsed or refractory CLL. The trial included 335 relapsed or refractory CLL patients at least 18 years of age who were randomly assigned to either four to six cycles of fludarabine plus alemtuzumab (n = 168) or fludarabine alone (n = 167). After a median follow-up of 29.5 months, patients receiving additional alemtuzumab showed a statistically significantly improved OS (HR = 0.65, 95% CI = 0.45 to 0.94, \( P = .021 \)) and PFS (HR = 0.61, 95% CI = 0.47 to 0.80, \( P = .0003 \)). Treatment with alemtuzumab caused more AEs (98% fludarabine + alemtuzumab arm vs 90% fludarabine arm, \( P \) value not provided) and serious AEs (33% fludarabine + alemtuzumab arm vs 25% fludarabine arm, \( P \) value not provided), but deaths caused by AEs were similar between both groups (6% fludarabine + alemtuzumab arm vs 7% fludarabine arm, \( P \) value not provided).

Implication for Practice.
This trial was able to demonstrate an improved OS and PFS by the additional administration of alemtuzumab compared with fludarabine alone in patients with relapsed or refractory CLL.

Trial 9: Low-dose decitabine vs best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group

MDS is a heterogeneous group of disorders that are characterized by myeloid, erythroid, or megakaryocytic dysplasia, or a combination of dysplasias, associated with ineffective hematopoiesis and a high rate of transformation to AML, approximately in 20% of patients. The main treatment approach for higher-risk (International Prognostic Scoring System: intermediate- and high-risk) MDS patients is intensive chemotherapy with allogeneic stem cell transplantation (alloSCT). Unfortunately, not all patients are eligible for alloSCT because of the lack of an available donor or because of patient characteristics such as performance status, the presence of major comorbid conditions, or patient age. There were several treatment options for patients who were not eligible for alloSCT including best supportive care (BSC), low-dose cytarabine and hypomethylating agents such as 5-azacitidine and decitabine. The trial by Lübbert et al. [7] compared low-dose decitabine with BSC in previously treated higher-risk patients with MDS who are older than 60 years of age and not eligible for intensive chemotherapy.
This multicenter trial included 233 patients, randomly assigned to either eight to ten courses of low-dose decitabine (n = 119) or BSC (n = 114). After a median follow-up time of 2.5 years, patients receiving decitabine showed a statistically significantly improved PFS (HR = 0.68, 95% CI = 0.52 to 0.88, P = .004) and statistically significantly decreased cumulative incidence of AML (22% vs 33% at 1 year and 30% vs 43% at 2 years, P = .036). Furthermore, 13% of the patients who received decitabine achieved CR compared with none in the BSC group. However, this did not lead to a statistically significant difference between both arms in OS (HR = 0.88, 95% CI = 0.66 to 1.17, P = .38). Treatment with decitabine caused more infections (WHO grade 3 or 4: 58% decitabine arm vs 50% BSC arm, P value not provided), more febrile neutropenia (WHO grade 3 or 4: 25% decitabine arm vs 7% BSC arm, P value not provided), but fatigue was decreased by decitabine (WHO grade 3 or 4: 9% arm decitabine vs 14% BSC arm, P value not provided). Furthermore, the study assessed quality of life on a self-reported voluntary approach.

Implication for Practice.
This trial was able to show the clinical benefit (longer PFS and lower incidence of AML) of low-dose decitabine compared with BSC for patients with higher-risk MDS who are older than 60 years of age and not eligible for intensive chemotherapy. However, there was no statistically significant difference in OS between the two treatment arms.

Reviews and Protocols in the Cochrane Library
In the latest issues of the Cochrane Library (Issue 3, 2011–Issue 10, 2011; see www.thecochranelibrary.com), 6 new reviews, 2 review updates and 16 new protocols were published.

New Review 1: Vaccines for prophylaxis of viral infections in patients with hematological malignancies

Clinical Background.
Immunocompromized patients with hematological malignancies are at higher risk of viral infections, which might lead to morbidity or even death. Some infections result in hospitalization of the patient. Vaccinations in healthy people and children can prevent viral infections such as influenza, varicella, or herpes zoster, but it is unclear whether the evidence is strong enough to show clinically relevant effects of vaccination in hematological malignant patients. Therefore, the review by Cheuk et al. examines the efficacy and safety of viral vaccines in patients with hematological malignancies.

Contribution.
The review by Cheuk et al. included 8 RCTs with a total of 593 patients examining heat-inactivated varicella zoster virus vaccine (2 trials), influenza vaccines (5 trials) and inactivated poliovirus vaccine (1 trial). No RCTs on other viral vaccines, such as hepatitis A, hepatitis B, measles, mumps, or rubella, were found.

Treatment with varicella zoster virus vaccine compared with no vaccine reduced the incidence of herpes zoster virus (risk ratio [RR] = 0.54, 95% CI = 0.3 to 1.0, P = .05), although the reduction was not statistically significant; also, statistically significantly more local AEs were
observed (RR = 20.94, 95% CI = 2.88 to 152.36, \( P = .003 \)). With the vaccine, the severity of herpes zoster in adults with lymphoma or leukemia might be reduced if given before and after stem cell transplantation\(^{35,36}\).

The trials comparing influenza vaccine with no vaccine (assessed by two trials) did not provide information on incidence of influenza, the primary outcome of the review, but showed statistically significantly fewer respiratory infections (RR = 0.39, 95% CI = 0.19 to 0.78, \( P = .008 \)) as well as hospitalizations (RR = 0.17, 95% CI = 0.09 to 0.31, \( P < .00001 \)\(^{37,38}\)). Patients receiving influenza vaccine experienced a statistically significantly higher frequency of irritability (\( P = .04 \)) and local AEs (\( P = .002 \)). No statistically significant differences in seroconversion were observed in patients who received the influenza vaccine, regardless of administration of one or two doses (one trial)\(^{39}\), when given as recombinant or standard influenza vaccine (one trial)\(^{40}\), or when given with or without reinduction chemotherapy (one trial)\(^{41}\). The one trial that compared inactivated poliovirus vaccine starting at 6 vs 18 months after stem cell transplantation did not report a statistically significant difference in seroconversion\(^{42}\).

**Implications for Practice.**
The quantity and quality of available evidence was very low, and further RCTs are needed to evaluate the clinical impute of viral vaccines in patients with hematological malignancies.

**New Review 2: Treatment for disseminated intravascular coagulation in patients with acute and chronic leukemia**\(^{13}\)

**Clinical Background.**
Disseminated intravascular coagulation is the activation of coagulation in blood vessels throughout the body, leading to organ dysfunction and bleeding with a high risk of death. It may occur in the course of severe diseases, e.g. acute or chronic leukemia, and can lead to severe complications. The Cochrane Review by Martí-Carvajal et al.\(^{13}\) focused on the clinical efficacy and safety of any pharmacological intervention for the treatment of disseminated intravascular coagulation in patients with acute or chronic leukemia.

**Contribution.**
The review by Martí-Carvajal et al.\(^{13}\) included four RCTs with 126 patients. Two RCTs were conducted in patients with leukemia assessing tranexamic acid and dermatansulphate, whereas the other two trials analyzed mixed population of patients who did or did not have leukemia. Of these, one RCT assessed human activated protein C compared with heparin (only 55 [55%] leukemia patients among 104 patients) and the other trial analyzed recombinant human soluble thrombomodulin compared with heparin (only 104 [44%] leukemia patients among 234 patients). For these two trials, data were not reported for the leukemia subgroups. Overall mortality and in-hospital mortality from any cause and bleeding were the primary endpoints of this systematic review. Overall mortality was not assessed by any of the included RCTs. The two RCTs that included only leukemia patients were very small. One RCT included 10 patients with leukemia and compared dermatan with heparin. It reported no deaths during study treatment and stated that hemorrhagic diathesis improved rapidly in the patients at study entry, except for one patient in
the heparin group. Safety was not reported in this RCT. The other RCT included 12 patients and compared tranexamic acid with placebo. It reported that bleeding severity diminished rapidly in the tranexamic acid group, although hemorrhage persisted in the placebo group (without any further information). Furthermore, there were no thromboembolic complications in tranexamic acid or placebo group.

**Implications for Practice.**
To date, it is not possible to determine whether any supportive anticoagulant approach with human activated protein C, recombinant human soluble thrombomodulin, tranexamic acid, or dermatansulfate is effective or harmful for patients presenting with disseminated intravascular coagulation related to acute or chronic leukemia. There is an urgent need for sufficiently powered RCTs to test the effects of the available treatment approaches.

**New Review 3: TPO receptor agonist for chronic idiopathic thrombocytopenic purpura** [15]

**Clinical Background.**
Chronic idiopathic thrombocytopenia purpura (ITP) is an autoimmune disorder with an abnormally low platelet count because of antibodies that destroy platelets. So far, the mainstay of therapies for ITP, such as corticosteroids, intravenous immunoglobulins, and splenectomy, aimed to reduce platelet destruction. A new developed treatment approach focused on increasing platelet counts by the stimulation of the thrombopoietin (TPO) receptor through a synthetic TPO receptor agonist such as romiplostim or eltrombopag. This systematic review summarizes the available evidence on the role of TPO receptor agonists in chronic ITP.

**Contribution.**
Zeng et al. [15] included six RCTs that included 808 patients in their systematic review. Five RCTs compared TPO receptor agonists with placebo, and one trial compared TPO receptor agonists to standard of care. The authors of the review could not find evidence to support the efficacy of TPO receptor agonists in the treatment of chronic ITP.

OS, the primary outcome of this systematic review, was not assessed in any of the included RCTs. TPO receptor agonists vs placebo improved significantly the complete response rate (RR = 9.29, 95% CI = 2.32 to 37.15), overall platelet response rate (RR = 4.06, 95% CI = 2.93 to 5.63, \( P < .00001 \)), and overall bleeding events rate (WHO grades 1 to 4: RR = 0.78, 95% CI = 0.68 to 0.89). No statistically significant difference in bleeding events compared with placebo (RR = 0.48, 95% CI = 0.20 to 1.15, \( P = .10 \)) or compared with standard of care (RR = 0.49, 95% CI = 0.15 to 1.63, \( P = .24 \)) was revealed. The total amounts of all AEs as well as of serious AEs were not statistically significantly different between the treatment (\( P = .35 \)) and placebo group (\( P = .68 \)). With TPO receptor agonists, the overall platelet response was statistically significantly improved (RR = 1.81, 95% CI = 1.37 to 2.37, \( P < .0001 \)), and statistically significantly fewer serious AEs occurred compared with standard of care (RR = 0.61, 95% CI = 0.40 to 0.92, \( P = .02 \)).

**Implications for Practice.**
The available evidence showed that TPO receptor agonists did not improve the incidence of statistically significant bleeding events (ie, severe, life-threatening, or fatal bleedings) in patients with chronic ITP. Further research is needed to assess the effect on OS.
New Review 4: Comparison of chemotherapy including escalated BEACOPP vs chemotherapy including ABVD for patients with early unfavorable or advanced stage Hodgkin lymphoma [10]

Clinical Background.
Hodgkin lymphoma, a malignancy of the lymphatic system, is a potentially curable lymphoma and one of the most common cancers in young adults. Treatment is with multiagent chemotherapy with or without radiation. Finding the best treatment with the greatest efficacy and least toxic effects is the main challenge. Two different international standards for the treatment of early unfavorable and advanced stage HL are available: chemotherapy with BEACOPP escalated and chemotherapy with ABVD.

Contribution.
This review by Bauer et al. [10] included four RCTs with a total of 2868 patients with previously untreated, early unfavorable, or advanced stage HL. The included RCTs restricted the age of the study population from 16–60 years of age. So far, the review could not conclusively answer the question which chemotherapy regimen provides the greatest efficacy with least disadvantages. Treatment with BEACOPP escalated statistically significantly improved PFS (HR = 0.53, 95% CI = 0.44 to 0.64, \( P < .001 \)) but did not result in a statistically significant difference in OS (HR = 0.80, 95% CI = 0.59 to 1.09, \( P = .16 \)). Furthermore, the BEACOPP escalated regimen caused statistically significantly more WHO grade III or IV hematological toxicities (anemia: \( P < .001 \); infection: \( P < .001 \); leucopenia: \( P < .001 \); neutropenia: \( P = .007 \); and thrombocytopenia: \( P < .001 \)), which did not lead to statistically significant differences in treatment-related mortality (\( P = .29 \)) or occurring secondary malignancies (\( P = .83 \)). However, trials did not provide sufficient information to judge the effects on quality of life as well as long-term toxic effects (eg, fertility, cardiac toxicity).

Implications for Practice.
The authors concluded that adult patients younger than 60 years of age who had early unfavorable or advanced stage HL benefited from chemotherapy including BEACOPP escalated regarding PFS, but no statistically significant difference in OS was demonstrated. A longer follow-up and the inclusion of currently ongoing studies (eg, the EORTC 20012 trial) will lead to a more definitive answer with respect to OS.


Clinical Background.
AML is characterized by a rapid proliferation of nonfunctional myeloblasts in the bone marrow, leading to anemia, infections, and strong bleeding because of functional pancytopenia. If possible, patients with AML should be treated with high-intensive chemotherapy regimens (with or without bone marrow transplantation), which lower the white blood cell count and disrupt the immune system. Subsequent infections are a main cause of mortality. Colony-stimulating factors (CSFs), including granulocyte-CSF (G-CSF) and granulocyte macrophage-CSF (GM-CSF), are administered to increase white blood cell count and result in a reduction of occurring infections.
This review by Gurion et al. [12] focuses on the impact of CSFs during and after chemotherapy in patients with AML.

**Contribution.**
The authors of the review included 19 RCTs including 5256 patients with AML, adults as well as children, in all treatment stages. Seventeen RCTs included patients who received one induction, one RCT in which patients received consolidation therapy, and one RCT that included patients who received salvage chemotherapy. Five RCTs assessed GM-CSF; 14 RCTs assessed G-CSF in the trials. However, all trials were pooled together and showed no evidence to support clinical relevant benefits of treatment with CSF. The review reported all-cause mortality (RR = 1.01, 95% CI = 0.98 to 1.05, \( P = .55 \), from 14 RCTs) and OS (HR = 1.00, 95% CI = 0.93 to 1.08, \( P = .96 \), from 11 RCTs) were similar between the two treatments. All-cause mortality at 30 days (RR = 0.97, 95% CI = 0.80 to 1.18, \( P = .75 \)), DFS (HR = 1.00, 95% CI = 0.90 to 1.13, \( P = .94 \)), and response rates (RR = 1.03, 95% CI = 0.99 to 1.07, \( P = .20 \)) were similar for the study arms. The additional administration of CSF did not decrease the occurrence of bacteremias (RR = 0.96, 95% CI = 0.82 to 1.12, \( P = .58 \)) nor invasive fungal infections (RR = 1.40, 95% CI = 0.90 to 2.19, \( P = .13 \)). The benefit of treatment with either G-CSF or GM-CSF seemed to be limited to the reduction of days in which patients were neutropenic. The median duration of neutropenia ranged from 7–26 days in the G-CSF and GM-CSF treatment arms, and between 16 and 30 days in the control arm. G-CSF and GM-CSF statistically significantly shortened the duration of neutropenia in all studies except for one, but a meta-analysis investigating this outcome was not conducted because of the variability in data reporting.

**Implication for Practice.**
The authors of this review concluded that the addition of CSFs to chemotherapy should not be given routinely to AML patients post-chemotherapy because these do not affect OS or infectious parameters, including the rate of bacteremias and invasive fungal infections.

**New Review 6: Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first CR [14]**

**Clinical Background.**
ALL is a hematologic malignancy characterized by a monoclonal proliferation, expansion, accumulation of immature lymphoid cells in the bone marrow, blood, and other organs. Although the majority of adults, approximately 90%, go into CR because of multi-agent chemotherapy regimens, the choice of subsequent consolidation and maintenance therapy is an area of uncertainty. Therapeutic alternatives include consolidation chemotherapy, ASCT and alloSCT. Pidala et al. conducted a systematic review with meta-analysis to synthesize the available evidence on “donor” (alloSCT) compared with “no donor” treatment approaches (consisting of chemotherapy or ASCT) in adults with ALL in the first CR (CR1).

**Contribution.**
This systematic review included 14 RCTs with 3157 patients (with standard-risk and high-risk ALL). Patients receiving alloSCT showed statistically significantly improved OS (HR = 0.86; 95% CI = 0.77 to 0.97, \( P = .01 \); the test of differences between high-risk and standard-risk ALL...
subgroups showed no statistically significant difference, \( P = .35 \) as well as DFS (HR = 0.82; 95% CI = 0.72 to 0.94, \( P = .004 \)). Furthermore, patients had a statistically significant reduction in primary disease relapses (RR = 0.53; 95% CI = 0.37 to 0.76, \( P < .001 \)). However, the nonrelapse mortality was also statistically significantly increased in the alloSCT arm (RR = 2.8; 95% CI = 1.66 to 4.73, \( P = .001 \)).

**Implications for Practice.**
The authors conclude that match sibling donor alloSCT is the optimal postremission therapy in patients with ALL older than 15 years of age. The OS, DFS, and risk of disease relapse were improved in this treatment arm. However, alloSCT increased the nonrelapse mortality. Further data on AEs were not assessed by the review.

**New Protocols**
There were 16 new protocols for Cochrane Reviews published:
Bergenthal N, et al. “The role of physical exercise for adult patients with haematological malignancies” [16]
Hutzschenreuter et al. “Granulocyte and granulocyte-macrophage colony stimulating factors for newly diagnosed patients with myelodysplastic syndromes” [22]
Vidal L, et al. “Chlorambucil for the treatment of patients with chronic lymphocytic leukaemia, or small lymphocytic lymphoma” [27]
Bergner N, et al. “Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL)” [17]

**Updated Reviews**
There was one updated Cochrane Review published by Okebe et al. titled “Therapeutic interventions for Burkitt lymphoma in children” [44].
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