Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-098 Daratumumab

Stand: Juni 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Daratumumab + Bortezomib + Thalidomid + Dexamethason zur Behandlung des neu diagnostizierten multiplen Myeloms; Patienten, die für eine autologe Stammzelltransplantation geeignet sind.	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Autologe Stammzelltransplantation • Allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen (§ 35a SGB V): • Es liegen keine Beschlüsse vor. Beschlüsse über die Erteilung von Aufträgen an die Expertengruppen nach § 35c Abs. 1 SGB V: Beschluss vom 18.10.2018: • Bortezomib + Cyclophosphamid + Dexamethason zur Induktionstherapie des neu diagnostizierten multiplen Myeloms • Bortezomib + Lenalidomid + Dexamethason zur Induktionstherapie des neu diagnostizierten multiplen Myeloms Richtlinie Methoden Krankenhausbehandlung (Stand: 23. Februar 2018) – Methoden, deren Bewertungsverfahren ausgesetzt sind: Beschluss vom 19.01.2017: • Autologe Mehrfachtransplantation (Tandemtransplantation) bei Multiplem Myelom • Allogene Stammzelltransplantation bei Multiplem Myelom in der Erstlinientherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Daratumumab	Zugelassenes Anwendungsgebiet: Daratumumab in Kombination mit Bortezomib Thalidomid und Dexamethason für die Behandlung erwachsener Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzelltransplantation geeignet sind.
Chemotherapien	
Carmustin L01AD01 Carmubris®	CARMUBRIS ist zur unterstützenden Behandlung chirurgischer Operationen und Bestrahlungen, oder als Kombinationsbehandlung mit anderen Substanzen bei folgenden Gewebsneubildungen angezeigt: […] Multiples Myelom: in Kombination mit anderen Zytostatika und einem Nebennierenrindenhormon, besonders Prednison.
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: […] – Remissionsinduktion bei Plasmozytom (auch in Kombination mit Prednison)
Doxorubicin L01DB01 Adrimedac®	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: […] – Fortgeschrittenes multiples Myelom Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Melphalan L01AA03 Alkeran®	Multiples Myelom (Plasmozytom)
Vincristin L01CA02 Vincristinsulfat-Teva®	Vincristinsulfat-Teva® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: […] – multiplem Myelom
Weitere antineoplastische Arzneimittel	
Bortezomib L01XX32 Velcade®	VELCADE ist in Kombination mit Dexamethason oder mit Dexamethason und Thalidomid für die Induktionsbehandlung erwachsener Patienten mit bisher unbehandeltem multiplen Myelom indiziert, die für eine Hochdosis-Chemotherapie mit hämatopoetischer Stammzelltransplantation geeignet sind. […]

Lenalidomid L04AX04 Revlimid®	Multiples Myelom Revlimid als Monotherapie ist indiziert für die Erhaltungstherapie von erwachsenen Patienten mit neu diagnostiziertem multiplem Myelom nach einer autologen Stammzelltransplantation. […]
Immunstimulanzien	
Interferon alfa-2b L03A B05 IntronA®	Multiples Myelom Als Erhaltungstherapie bei Patienten, die nach einer initialen Induktions-Chemotherapie eine objektive Remission erreichten (mehr als 50%ige Reduktion des Myelomproteins). Gegenwärtige klinische Erfahrungen zeigen, dass eine Erhaltungstherapie mit Interferon alfa- 2b die Plateauphase verlängert; jedoch wurden Effekte auf die Gesamtüberlebenszeit nicht endgültig bewiesen. […]
Glucocorticoide	
Dexamethason H02AB02 Dexa-CT®	Onkologie Palliativtherapie maligner Tumoren Prophylaxe und Therapie von Zytostatikainduziertem Erbrechen im Rahmen antiemetischer Schemata
Prednisolon H02AB06 Decortin® H	Hämatologie/Onkologie: […] – akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom (DS: e) […] – Palliativtherapie maligner Erkrankungen Hinweis: Prednisolon kann zur Symptomlinderung, z. B. bei Inappetenz, Anorexie und allgemeiner Schwäche bei fortgeschrittenen malignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen.
Prednison H02AB07 Decortin®	Hämatologie/Onkologie: […] – akute lymphoblastische Leukämie, Morbus Hodgkin, Non-Hodgkin-Lymphome, chronische lymphatische Leukämie, Morbus Waldenström, multiples Myelom (DS: e) […] – Palliativtherapie maligner Erkrankungen Hinweis: Prednison kann zur Symptomlinderung, z. B. bei Inappetenz, Anorexie und allgemeiner Schwäche bei fortgeschrittenenmalignen Erkrankungen nach Ausschöpfung spezifischer Therapiemöglichkeiten angewendet werden. Einzelheiten sind der aktuellen Fachliteratur zu entnehmen.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-098 (Daratumumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse events
ASCT	autologous stem cell transplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
CI	Confidence Interval
CON	Consolidation
CR	Complete Response
Cy-Dex	cyclophosphamide plus dexamethasone
DAHTA	DAHTA-Datenbank
EFS	Event free survival
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GvHD	graft-versus-host disease
HDT	High dose therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LEN	Lenalidomide
MM	Multiples Myelom
MRD	Minimal Residual Disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nCR	Near Complete Response
NDMM	Newly diagnosed multiple myeloma
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall Survival
PAD	bortezomib, adriamycin and dexamethasone

PFS	Progression Free Survival
RCT	Randomized controlled trial
RR	Relative Risk
SIGN	Scottish Intercollegiate Guidelines Network
SPM	secondary primary malignancy
TRIP	Turn Research into Practice Database
TTP	Time to progression
VBMCP-VBAD-B	doxorubicin, dexamethasone/bortezomib
VCD	Bortezomib, cyclophosphamide and dexamethasone
VDCR	bortezomib, dexamethasone and lenalidomide
VGPR	very good partial response
VTD	bortezomib/thalidomide/dexamethasone
WHO	World Health Organization

1 Indikation

Anwendungsgebiet lt Beratungsanforderung: Daratumumab in Kombination mit Bortezomib Thalidomid und Dexamethason für die Behandlung erwachsener Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzelltransplantation geeignet sind.

Indikation für die Synopse: Zur Behandlung von erwachsenen Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzelltransplantation geeignet sind.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *multiplen Myelom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 15.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 569 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2017 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden Krankenhausbehandlung: Stammzelltransplantation bei Multiplem Myelom vom 19. Januar 2017.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 19. Januar 2017 beschlossen:

I. Die Richtlinie des G-BA zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung) in der Fassung vom 21. März 2006 (BAnz.2006 S. 4466), zuletzt geändert am 15. September 2016 (BAnz AT 22.12.2016 B2), wird wie folgt geändert:

In der Anlage II (Methoden, deren Bewertungsverfahren ausgesetzt sind) werden

1. im Abschnitt A (Aussetzung im Hinblick auf laufende oder geplante Studien) nach der Nummer 11.1 folgende Nummern 11.2 und 11.3 angefügt:

„11.2 Autologe Mehrfachtransplantation (Tandemtransplantation) bei Multiplem Myelom Beschluss gültig bis 30. Juni 2022

11.3 Allogene Stammzelltransplantation bei Multiplem Myelom in der Erstlinientherapie Beschluss gültig bis 30. Juni 2022 (verbunden mit Beschluss zur Qualitätssicherung gemäß § 136 SGB V)“

(…)

G-BA, 2017 [5]

Beschluss des Gemeinsamen Bundesausschusses über die Erteilung von Aufträgen an die Expertengruppen nach § 35c Abs. 1 SGB V (Expertengruppen Off-Label): Bortezomib + Cyclophosphamid + Dexamethason zur Induktionstherapie des neu diagnostizierten multiplen Myeloms sowie Bortezomib + Lenalidomid + Dexamethason zur Induktionstherapie des neu diagnostizierten multiplen Myelomsvom 18. Oktober 2018

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 18. Oktober 2018 beschlossen, die Expertengruppen Off-Label mit folgenden Bewertungen zum Stand der wissenschaftlichen Erkenntnisse zu beauftragen:

- Bortezomib + Cyclophosphamid + Dexamethason zur Induktionstherapie des neu diagnostizierten multiplen Myeloms

  sowie

- Bortezomib + Lenalidomid + Dexamethason zur Induktionstherapie des neu diagnostizierten multiplen Myeloms.

3.2 Cochrane Reviews

Scott K et al., 2016 [13].

Bortezomib for the treatment of multiple myeloma

Fragestellung

We assessed the effects of bortezomib treatment in comparison to other therapies, different doses, treatment administration and schedules of bortezomib, on overall survival (OS), progression free survival (PFS), response rate (RR), health-related quality of life (HRQoL), adverse events (AE) and treatment-related death (TRD).

Methodik

Population:

- Patients of any age, gender or ethnic origin and with any diagnosis of multiple myeloma. We included patients who were either newly diagnosed (had received no prior therapy) or patients with relapsed disease. We also included patients who were considered to be either transplant eligible or ineligible. Patient eligibility for stem cell transplant is determined primarily by age, as well as performance status, frailty, and presence of comorbidities. We did not define transplant eligibility for this review and therefore selected studies that included all types of patients.

Intervention/Komparator:

We included RCTs that investigated the following comparisons.

- Bortezomib versus no bortezomib with the samebackground therapy in each arm
- Bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent(s)
- Bortezomib dose comparisons and comparisons of different treatment administrations and schedules

Endpunkte:

- Overall survival (OS), PFS, ORR, PRR, TTP, CRR, AE, HRQoL

Recherche/Suchzeitraum:

- MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE (till 27 January 2016)

Qualitätsbewertung der Studien:

- Cochrane Approach

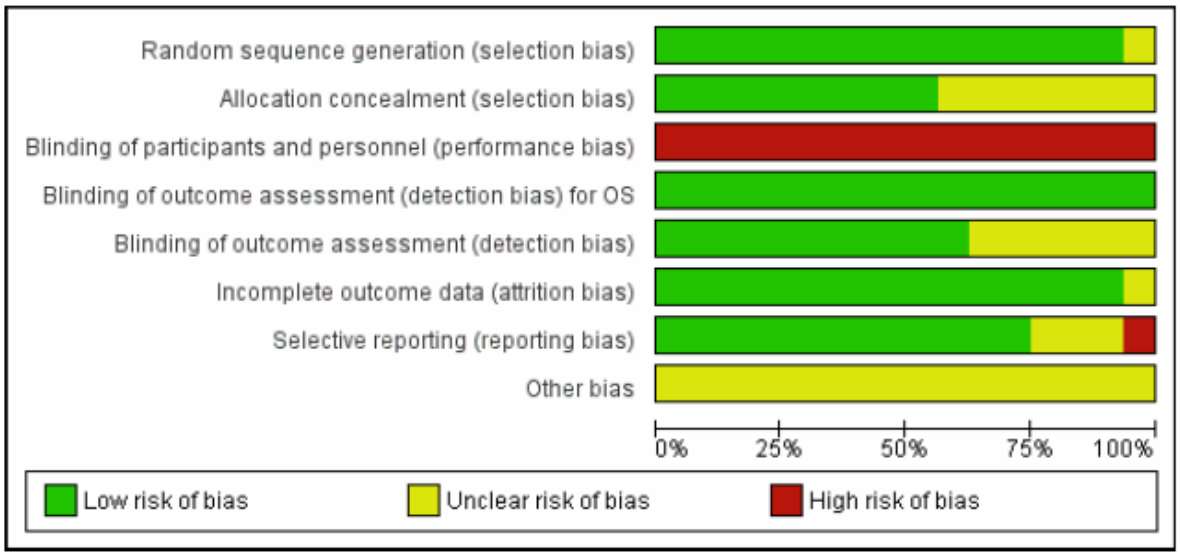
Ergebnisse

Anzahl eingeschlossener Studien:

- 6 relevant RCTs involving 5626 patients and included 12 trials
- All trials were randomised and open-label studies. Two trials were published in abstract form and therefore we were unable to assess potential risk of bias in full.

Qualität der Studien:

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

- There is moderate-quality evidence that bortezomib prolongs OS (four studies, 1586 patients; Peto OR 0.77, 95% CI 0.65 to 0.92) and PFS (five studies, 1855 patients; Peto OR 0.65, 95% CI 0.57 to 0.74) from analysing trials of bortezomib versus no bortezomib with the same background therapy in each arm.
- There is high-quality evidence that bortezomib prolongs OS (five studies, 2532 patients; Peto OR 0.76, 95% CI 0.67 to 0.88) but low-quality evidence for PFS (four studies, 2489 patients; Peto OR 0.67, 95% CI 0.61 to 0.75) from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent(s).
- We identified four trials in the meta-analysis that measured time to progression (TTP) and were able to extract and analyse PFS data for three of the studies, while in the case of one study, we included TTP data as PFS data were not available. We therefore did not analyse TTP separately in this review.
- Patients treated with bortezomib have increased risk of thrombocytopenia, neutropenia, gastro-intestinal toxicities, peripheral neuropathy, infection and fatigue with the quality of evidence highly variable.
- There is high-quality evidence for increased risk of cardiac disorders from analysing trials of bortezomib versus no bortezomib with different background therapy in each arm or versus other agents.
- The risk of TRD in either comparison group analysed is uncertain due to the low quality of the evidence.
- Only four trials analysed HRQoL and the data could not be meta-analysed.

Subgroup analysis - disease setting

- We considered three subgroups for myeloma disease setting: transplant eligible, transplant ineligible and relapsed/refractory disease and included 11 trials in this subgroup analysis (we did not include the All India Institute Study as the disease setting was unclear).
  - For OS, a statistically significant benefit with bortezomib treatment was observed in all groups, with the smallest benefit observed in the transplant eligible group. Considering this group alone, the benefit was not statistically significant with a Peto odds ratio (OR) of 0.86 (95% CI 0.73 to 1.02) (Analysis 2.1). For PFS, the observed benefit for bortezomib was lower in the transplant eligible group than the other two groups but still statistically significant (Analysis 2.2). There was evidence of heterogeneity between subgroups for PFS (P = 0.002, I^2 = 84.5%).

Subgroup analysis - therapy setting

- We considered three subgroups for myeloma therapy setting: induction, consolidation and maintenance and included six trials in the subgroup analysis for therapy setting.
  - A statistically significant benefit for bortezomib was observed in all outcomes and subgroups except for OS following consolidation therapy. Heterogeneity tests between subgroups were non-significant for all outcomes.

Anmerkung/Fazit der Autoren

Patients receiving bortezomib had better response rates, longer time without progression and appeared to live longer compared to those not receiving bortezomib, however patients receiving bortezomib experienced more side effects. Other proteasome inhibitor drugs have also been developed, therefore further research should focus on whether these newer drugs provide additional benefits and fewer side effects than bortezomib. More studies on health-related quality of life are also needed.

3.3 Systematische Reviews

Al-Ani F et al., 2017 [1].

Post-transplant consolidation plus lenalidomide maintenance vs lenalidomide maintenance alone in multiple myeloma: A systematic review

Fragestellung

to compare the efficacy of post-ASCT consolidation plus lenalidomide maintenance (CON+LEN) vs lenalidomide maintenance alone (LEN alone) in NDMM.

Methodik

Population:

- adult patients with NDMM treated with ASCT

Intervention/Komparator:

- LEN maintenance following transplant with or without post-transplant consolidation or LEN maintenance alone

Endpunkte:

- PFS, OS, CR, MRD, adverse events

Recherche/Suchzeitraum:

- a systematic literature search to identify potential studies in MEDLINE (1946 to 2015), EMBASE (1946 to 2015), CENTRAL (1946 to 2015) using an OVID interface (1946 to 2015). The search was conducted in April 2016 and updated in May 2017

Qualitätsbewertung der Studien:

- The methodological quality of the selected single arm phase II studies was assessed according to Newcastle-Ottawa Quality Assessment Scale.

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen studies were included with 2275 participants with NDMM treated with ASCT and lenalidomide maintenance

Qualität der Studien:

- Overall, the risk of bias for the included RCT was low. However, it is noteworthy to state that the adequate sequence generation, allocation concealment and blinding of participants were unclear in most RCTs. The methodological quality of single arm phase II studies was good in regards to representativeness of exposed cohort and adequacy of follow-up. Nevertheless, overall, the missing information in the 7 included abstracts hampers proper assessment of studies' quality.

Studienergebnisse:

- Two groups were identified: CON+LEN group (n = 1102) and LEN alone group (n = 1173).

- No statistically significant difference in the complete response rate between the two groups.
- Interestingly, we found that very good partial response or better rate is around 1.5-fold significantly higher in the CON+LEN group compared to LEN alone group [RR: 1.46; 95% CI: 1.25-1.70; P < .0001].
- No significant difference between the two groups regarding PFS and OS at 3-4 years follow-up.
- The risk of secondary primary malignancy (SPM) was also similar between the two groups. Data on adverse events were limited.

Anmerkung/Fazit der Autoren

We acknowledge that the data we are presenting in this systematic review are still immature, as the included studies report on 3 to 4 years of follow-up only. It is still too soon for anyone to draw any firm conclusion about the usefulness of consolidation therapy post-transplant. Overall, our analysis demonstrated deepening of the responses with consolidation, but this did not translate into improved PFS and OS; however, the benefit of depth of response was not confirmed by MRD negativity due insufficient data. The risk of toxicities associated with additional consolidation therapy should also be considered. Future studies on post-transplant consolidation should highlight the MRD and survival endpoints, as well as the risk stratification for potential individualized decisions on consolidation treatment.

Liu X et al., 2017 [8].

Comparing efficacy and survivals of initial treatments for elderly patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials.

Fragestellung

to evaluate the efficacy and clinical outcome of initial therapies for elderly patients with multiple myeloma (MM).

Methodik

Population:

- elderly patients with newly diagnosed MM who were unsuitable for HDT.

Intervention/Komparator

- initial therapy for MM patients

Endpunkte:

- CR/nCR, ORR, PFS and OS

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library and the Science Citation Index as well as relevant websites until 2015

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 19 RCTs containing 7,235 participants and 17 treatments.

Qualität der Studien:

- Jadad Scale: maximal score for an included study was 5 and studies were classified on the basis of quality as high (score: 3–5) versus low (score: 0–2).
  - o

Studienergebnisse:

- As compared to the classic melphalan plus prednisone (MP) regimen, the majority of other initial regimens showed higher rates of complete response/near complete response, overall response rate (ORR) and better PFS as well as OS
  - o These four outcomes favored the two lenalidomide plus dexamethasone regimens (continuous lenalidomide and 18 cycles of lenalidomide plus dexamethasone), especially continuous lenalidomide plus dexamethasone regimen, over the majority of other regimens including the two established standard treatments (MP plus thalidomide or bortezomib) for elderly patients with newly diagnosed MM.

Anmerkung/Fazit der Autoren

Our NMA demonstrated that the two lenalidomide plus dexamethasone initial treatments (18 cycles of lenalidomide plus dexamethasone and continuous lenalidomide plus dexamethasone), especially the continuous lenalidomide plus dexamethasone, resulted in better efficacy and prognosis for the elderly patients with MM.

Liu X et al., 2015 [9].

Bortezomib-based vs non-bortezomib-based post-transplantation treatment in multiple myeloma patients: a systematic review and meta-analysis of Phase III randomized controlled trials.

Fragestellung

to evaluate the efficacy and safety of bortezomib-based vs non-bortezomib-based post-transplantation therapy in patients with multiple myeloma.

Methodik

Population:

- the participants were patients with newly diagnosed MM of any stage and who had been treated with induction chemotherapies followed by ASCT.

Intervention:

- bortezomib-containing regimens

Komparator:

- placebo or other non-bortezomib-containing regimens

Endpunkte:

- PFS/EFS (event-free survival), OS as well as response rate of CR/nCR, VGPR (very good partial response), and PR (partial response), adverse events

Recherche/Suchzeitraum:

- PubMed, EMBASE, the Cochrane Library and the Science Citation Index, and other relevant websites until 2014

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- Three randomized controlled trials comprising 1,518 participants.

Qualität der Studien:

- the maximal score for an included study was 5 and studies were classified on the basis of quality as high (score: 3–5) vs low (score: 0–2).

Studienergebnisse:

- ORR:
  - The adjusted pooled OR for overall response rate (CR/nCR+VGPR+PR) was 1.85 (95% CI: 1.29–2.64), and the pooled ORs for consolidation and maintenance therapy studies were 1.63 (95% CI: 0.81–3.82) and 1.93 (95% CI: 1.28–2.92), respectively.
  - Moreover, from the cumulative forest plot, OR has an increasing trend as consolidation studies are added. Pooled OR from cumulative analysis of consolidation therapy was 1.63 (95% CI: 0.81–3.82), and no significant difference was found. After adding the maintenance treatment study conducted by Pieter Sonneveld, the OR was larger than 1 (OR =1.85, 95% CI: 1.29–2.64).
  - On the other hand, our integrate analysis demonstrated that the rate of CR/nCR in bortezomib-based groups was significantly higher than that in non-bortezomib-based groups (53.0% vs 39.8%, *P*,0.001), and the pooled OR for the rates of CR/nCR was 1.75 (95% CI: 1.42–2.15), and the pooled ORs for consolidation and maintenance therapy studies were 1.62 (95% CI: 1.18–2.22) and 1.86 (95% CI: 1.40–2.46), respectively. Meanwhile, the cumulative meta-analysis indicated that the beneficial effect of bortezomib-based post-transplantation treatment was more obvious when it was administrated as maintenance treatment with more narrow confidence interval (OR =1.75, 95% CI: 1.42–2.15 vs OR =1.62, 95% CI: 1.18–2.22).
- PFS:
  - All the included three trials reported PFS, and the pooled HR for PFS shown in Figure 3A was 0.73 (95% CI: 0.67–0.81), indicating that there was a 27% reduction in the risk of disease progression or death with bortezomib-based therapy after ASCT.
  - Moreover, the pooled ORs for consolidation and maintenance therapy studies were 0.73 (95% CI: 0.65–0.81) and 0.75 (95% CI: 0.63–0.90), respectively. Meanwhile, pooled HR from the cumulative meta-analysis for PFS confirmed the beneficial effect of bortezomib-based over non-bortezomib-based post-transplantation therapy.

- OS:
  - All the three trials reported 3-year OS, and all the trials claimed that there was no statistical difference between experimental and control groups, which is consistent with our traditional and cumulative meta-analysis (HR for 3-year OS was 0.78, 95% CI: 0.57–1.06, *P*=0.90)
  - The pooled HRs for consolidation and maintenance therapy studies were 0.81 (95% CI: 0.53–1.25) and 0.75 (95% CI: 0.48–1.16), respectively.
- Adverse events:
  - Incidence rates of overall adverse events and grade 3 and 4 peripheral neuropathy were similar in the bortezomib-based groups and the non-bortezomib-based groups (P=0.12 and P=0.41, respectively).

Anmerkung/Fazit der Autoren

In conclusion, post-transplantation therapy (especially maintenance therapy) with bortezomib-based regimen contributes to improved response rate and PFS with a favorable safety profile. However, prolonged follow-up period is required to confirm the beneficial effect of bortezomib-based post-transplantation therapy conferred on OS.

Zeng ZH et al., 2017 [17].

Induction regimens for transplant-eligible patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials.

Fragestellung

to compare the early efficacy and survivals of induction regimens for transplant-eligible patients with untreated multiple myeloma.

Methodik

Population:

- the participants were transplant-eligible patients with newly diagnosed MM

Intervention/Komparator:

- different pre-ASCT induction therapies

Endpunkte:

- ORR, PFS, OS

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library until 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool for assessing the risk of bias was used to evaluate the quality of the included trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 RCTs that included 4,763 patients were analyzed

Qualität der Studien:

- The included RCTs had low risks of selection bias about random sequence generation, attrition bias, reporting bias, and other biases, in which the rates of low risk were 100%, 92.3%, 92.3%, and 76.9%, respectively. Studies without clear information on allocation concealment, performance bias and detection bias accounted for 53.8%, 92.3%, and 92.3%, respectively.

Studienergebnisse:

- Netzwerkmetaanalyse:
  - 13 included trials were able to be used to evaluate ORR: For the pairwise comparison of regimens, VTD had significantly higher ORR than other regimes, except for VDCR and VDR to which the superiority was non-significant. VDR, VDCR, VDC, VD, VBMCP-VBAD-B, TD, RD, and PAD had significantly higher ORR than VAD, Dex, and Cy-Dex. TAD showed significantly higher ORR than Cy-Dex and VAD, but had significantly poorer ORR than PAD, VBMCP-VBAD-B, VDC, VDCR, VDR, and VTD. Meanwhile, VDCR had significantly higher ORR than VDR. VBMCP-VBAD-B resulted in significantly better ORR than VD and TD. No statistically significant difference was found for other comparisons. VTD was ranked the best regimen in terms of ORR.
  - Eight studies involving 10 regimens were included in NMA for OS: Results showed that VTD was significantly better than TAD and VAD, and PAD was also significantly superior to VAD. Meanwhile, Cy-Dex had a shorter OS than the other nine regimens. On the other hand, there was no statistically significant difference among VTDC, Cy-Dex, Dex, VD, VBMCP-VBAD-B, PAD, VTD, and TD. VTDC was ranked the best regimen for OS with relatively higher probability.
  - Eight out of 14 trials reported data on PFS: PAD, VD, VTD, VBMCP-VBAD-B, TAD, and VTDC had significant superiority when compared with TD (Table S3). PAD, VD, VTD, VBMCP-VBAD-B, TAD, and VTDC had significantly better PFS than TD. Furthermore, TAD and PAD resulted in significantly better PFS than VAD. VBMCP-VBAD-B had significantly better PFS than VTD. No statistically significant difference was found for other comparisons. TAD was ranked the best regimen for PFS with relatively higher probability.

Anmerkung/Fazit der Autoren

The NMA demonstrated that the VTD, VTDC, and TAD regimens are most beneficial in terms of ORR, OS, and PFS for transplant-eligible patients with NDMM, respectively.

Kommentare zum Review

- Many comparisons in the NMA were based on single study
- the survival of NDMM could be influenced by transplantation schemes, consolidation therapy, and maintenance therapy

Jain T et al., 2019 [7].

High-Dose Chemotherapy with Early Autologous Stem Cell Transplantation Compared to Standard Dose Chemotherapy or Delayed Transplantation in Patients with Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis.

Fragestellung

to examine patterns of OS and PFS with the early SCT versus SDT/late SCT approaches in patients with newly diagnosed MM.

Methodik

Population:

- patients (OS and PFS) who underwent early SCT versus SDT/late SCT, in patients with newly diagnosed MM

Intervention/Komparator:

- SCT versus SDT/late SCT

Endpunkte:

- OS, PFS and treatment-related mortality (TRM)

Recherche/Suchzeitraum:

- A literature search was conducted from database inception through October 1, 2017, with electronic databases such as MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment

Ergebnisse

Anzahl eingeschlossener Studien:

- 3633 patients were included in the analysis of these 12 studies, including 1822 who underwent early SCT and 1811 who underwent SDT/late SCT. All studies were randomized control trials that enrolled patients with newly diagnosed MM.

Qualität der Studien:

- The risk of bias assessment using the Cochrane risk of bias tool showed a moderate risk of bias overall

Studienergebnisse:

- OS: no statistically significant differences in OS between the 2 approaches
  - To establish the robustness of this analysis, we performed sensitivity analysis by removing individual studies. Removing IFM 9906 changed the HR to .81 (95% CI, .68 to .97), which was then favorable toward early SCT.
  - We also performed a sensitivity analysis after exclusion of studies that performed tandem transplantation as a part of the HDT/SCT. There was no change in the overall outcome of OS.

- PFS (reported in all studies): combined analysis revealed a statistically significant benefit with the early SCT approach (HR, .67; 95% CI, .54 to .82).
  - In a sensitivity analysis, exclusion of individual studies did not change in the overall outcome of PFS, which remained favorable toward an early SCT approach. On exclusion of the 4 studies that used a tandem transplantation approach, PFS remained significantly favorable toward the early SCT arm (combined HR, .69; 95% CI, .60 to .79).
- Use of Novel Agents: A subgroup analysis was conducted for the 3 studies including novel agents with the induction regimen. The novel agents included in these studies were lenalidomide alone in 2 studies and a combination of lenalidomide and bortezomib in 1 study. The IFM9906 study used a novel agent, thalidomide, in the SDT arm; however, this was not included in the subgroup of novel agents, because thalidomide was used only in the SDT arm, whereas patients in the early SCT arm received vincristine, adriamycin, and dexamethasone as induction therapy.
  - OS remained statistically non-significant between the early SCT and SDT/late SCT arms in the combined analysis of studies using novel agents. In studies not using novel agents for induction therapy, OS was still not statistically significantly different (Figure 3). PFS analysis showed a combined HR of .50 (95% CI, .36 to .70) for the 3 studies, indicating the statistically significant advantage of the early SCT approach (Figure 4). In the studies in which no novel agents were used in induction regimens, PFS was still statistically significantly better in the early SCT arm (HR, .73; 95% CI, .58 to .93).
- TRM and Response Rates: TRM has improved in the more recent studies compared with older studies; with less use of the more toxic traditional chemotherapy and improved supportive care. In the more recent studies, TRM with either approach was low, <2 %. Complete response and overall response rates remained better with the early SCT approach.

Anmerkung/Fazit der Autoren

The data from our meta-analysis show a PNS benefit but no OS benefit of an early SCT approach in patients with newly diagnosed MM. In the studies using novel agents, a statistically significant PFS benefit but not a statistically significant OS benefit, possibly owing to limited follow-up in some recent studies. Although SCT should be offered to all transplantation eligible patients with newly diagnosed MM, the advantage in the era of the novel agents will continue to be evaluated.

Sekine L et al., 2019 [14].

Frontline treatment for transplant-eligible multiple myeloma: A 6474 patients network meta-analysis.

Fragestellung

In order to define, among current and past available therapeutic options, the best frontline treatment approaches for patients eligible to autologous transplantation, we have conducted a systematic review and MTC meta-analysis comprising all available randomized clinical trials to date.

Methodik

Population:

- newly diagnosed transplant-eligible MM patients.

Intervention/Komparator:

- two or more therapeutic approaches for MM

Endpunkte:

- OS, PFS, CR, ORR, AEs

Recherche/Suchzeitraum:

- MEDLINE, Embase, LILACS, SciELO, Cochrane CENTRAL. The last date of the search was May 1st 2018.

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 clinical trial publications, enrolling 6474 patients and comparing 11 different treatment frontline setting regimens

Qualität der Studien:

- Overall, risk assessment was compromised by underreporting of randomization and concealment methods in most of the trials and non-blinding of participants and personnel.

TABLE 4 Quality assessment of included studies

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Early Interruption
Barlogie	2006-2008	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	No
Cavo	2010-2013	Low risk	Low risk	High risk	Unclear	Low risk	Low risk	No
Cook	2004	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	No
Lokhorst	2010	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	No
Ludwig	2013-2015	Unclear	Unclear	High risk	High risk	Low risk	Low risk	No
Morgan	2012	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	No
Pawlyn	2017	Low risk	Unclear	High risk	Unclear	Unclear	Unclear	No
Porter	2006-2007	Unclear	Unclear	High risk	Low risk	Unclear	Unclear	No
Sonneveld	2010-2015	Low risk	Low risk	High risk	Unclear	Low risk	Low risk	No
Straka	2016	Unclear	Unclear	High risk	Unclear	Unclear	Unclear	No

Studienergebnisse:

- OS analysis showed superiority of CRD (cyclophosphamide-lenalidomide-dexamethasone) over TD-based (thalidomide-dexamethasone, HR = 0.76,0.62-0.90), VAD-based (HR = 0.71,0.52-0.90), and Z-Dex (idarubicin-dexamethasone, HR = 0.37,0.17-0.76) regimens.
- Concerning PFS, VTD (bortezomib-thalidomide-dexametasone) showed superior results when compared with TD-based (HR = 0.66,0.51-0.84), VAD-based (HR = 0.61,0.46-0.82), Z-Dex (HR = 0.42,0.22-0.78), and high dose dexamethasone (Dex, HR = 0.62,0.41-0.90) regimens.
- Bortezomib/thalidomide regimens were not superior to lenalidomide, considering these outcomes.
- Also, concerning complete and overall response, VTD ranked first among other regimens, showing clear superiority over thalidomide-only containing protocols.
- Safety outcome evaluated infectious, cardiac, gastrointestinal, neurological, thrombotic, and hematological grade 3 to 4 adverse events.
- Risk of thrombotic events was higher with TAD (thalidomide-doxorubicin-dexamethasone), neurological with PAD (bortezomib-doxorubicin-dexamethasone), infectious with Dex, hematological with Z-Dex, gastrointestinal with VTD, and cardiac with PAD regimens.

Anmerkung/Fazit der Autoren

Our study endorses current recommendations on combined immunomodulatory drugs and proteasome inhibitors frontline regimens (in triplets) in transplant-eligible multiple myeloma patients, but also formally demonstrates the favorable performance of lenalidomide in overall and progression-free survival, when compared with bortezomib/thalidomide protocols.

Su B et al., 2018 [15].

A meta-analysis of autologous transplantation for newly diagnosed multiple myeloma in the era of novel agents.

Fragestellung

To evaluate the role of high-dose melphalan plus autologous stem-cell transplantation (ASCT) as consolidation therapy for patients with newly diagnosed multiple myeloma (NDMM) in the era of novel agents, we undertook this meta-analysis.

Methodik

Population:

- patients with NDMM

Intervention:

- high-dose melphalan plus ASCT

Komparator:

- novel agents containing consolidation (→ bortezomib, lenalidomide, or thalidomide containing regimens as consolidation therapy)

Endpunkte:

- OS and (or) PFS, AEs

Recherche/Suchzeitraum:

- Medline, Embase, the Cochrane controlled trials register, the SCI, ASH, EHA, and ASCO up to June, 2017.

Qualitätsbewertung der Studien:

- Ja, vermutlich Cochrane approach (s.u. Table 1)

Ergebnisse

Anzahl eingeschlossener Studien & Qualität der Studien:

- four RCTs: two trials evaluated outcomes from highdose melphalan plus ASCT versus alkylating agent-based regimens plus lenalidomide; two trials evaluated outcomes from high-dose melphalan plus ASCT versus bortezomib-based triplet regimens
- We also identified 10 single-arm prospective trials of ASCT alone covering 1907 subjects. These trials along with the above four RCTs only provided response quality data of pre-ASCT versus Post-ASCT

Table 1. The included RCTs characteristics of ASCT versus novel agents based consolidations.

Author/year	N		Regimen	Methodological quality					Follow-up period (M)
				GAS	AC	Blinding	DW	ITT	
RCTs of ASCT versus novel agent-based chemotherapy as consolidation therapy									
(1). RCTs of alkylating agent-based regimens plus lenalidomide									
Palumbo 2014 [10]	273	E	4 cycles RD, *2 cycles Mel200 and ASCT*, then R.	Yes	No	No	Yes	Yes	51.2
		C	4 cycles RD, *6 cycles MPR*, then R.						
Gay 2015 [11]	256	E	4 cycles RD, *2 cycles Mel200 and ASCT*, then RP or R.	Yes	No	No	Yes	Yes	52
		C	4 cycles RD, *6 cycles CDR*, then RP or R.						
(2). RCTs of ASCT versus Bortezomib-based triplet regimens									
Attal 2017 [12]	700	E	3 cycles RVD, *1 cycles Mel200 and ASCT +2 cycles RVD*, then R	Yes	No	No	Yes	Yes	43
		C	3 cycles RVD, *5 cycles RVD*, then R						44
Cavo 2016 [13]	1192	E	VCD induction, *1/2 cycles Mel_{200} and ASCT*, then R	Yes	No	No	Yes	Yes	34
		C	VCD induction, *4 cycles VMP*, then R						

E: experiment arm; C: control arm; RD: lenalidomide, dexamethasone; MPR: melphalan, prednisone, and lenalidomide; R: lenalidomide; RP: lenalidomide, prednisone; RVD: lenalidomide, bortezomib, and dexamethasone; VCD: bortezomib, cyclophosphamide, and dexamethasone; VMP: bortezomib, melphalan, and prednisone; GAS: generation of allocation sequence; AC: allocation concealment; DW: description of withdrawals; ITT: intension-to-treat analysis. M: months.

Studienergebnisse:

- Pooled analysis indicated that response quality improved further after ASCT in the era of novel agents (≥CR rates of 13% pre-ASCT versus 29% post-ASCT, p=.003).

- When compared to novel agents containing consolidation regimens, high-dose chemotherapy plus ASCT significantly improved progression-free survival (PFS) (HR =0.56, p<.001).
- No significant difference in overall survival (OS) was found between them (HR =0.66, p=.22). Of note, subgroup analysis indicated that ASCT could significantly improve OS (HR =0.49, p=.0004) when compared to alkylating agent-based regimens plus lenalidomide consolidation.

Anmerkung/Fazit der Autoren

In conclusion, response quality and PFS improved further over ASCT in the era of novel agents. The benefits with high-dose chemotherapy plus ASCT seemed to be more prominent when in comparison with alkylating agent-based regimens plus lenalidomide than bortezomib-based triplet regimens.

Yin X et al., 2018 [16].

Allogeneic stem-cell transplantation for multiple myeloma: a systematic review and meta-analysis from 2007 to 2017

Fragestellung

to evaluate the outcome of patients receiving allo-SCT and identified a series of prognostic factors that may affect the outcome of allo-SCT.

Methodik

Population:

- patients with multiple myeloma

Intervention:

- Treatment with allo-SCT

Komparator:

- Siehe Ergebnisteil

Endpunkte:

- OS. PFS, DFS, GvHD, relapse raste (RR), death rates and the 100-day, 1-, 2-, 3- and 5-year treatment-related mortality (TRM)

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library from 2007.01.01 to 2017.05.03.

Qualitätsbewertung der Studien:

- We followed 5 items to evaluate study quality: (1) conditioning regimens, (2) stem cell source, (3) donor, (4) GvHD prophylaxis regimen, and (5) disease status before allo-SCT. When articles provided one corresponding item, 1 was given to the study or otherwise 0. Only studies received 5 scores were deem as good quality, 4 scores were moderate quality and 3 scores were low quality.

Ergebnisse

Anzahl eingeschlossener Studien:

- 61 clinical trials involving 8698 adult patients

Qualität der Studien:

- According to quality assessment scores, 29 studies scored 5, 25 scored 4, and 7 scored 3.

Studienergebnisse:

- The pooled estimates (95% CI) for overall survival (OS) at 1, 2, 3 and 5 years were 70 (95% CI 56–84%), 62 (95% CI 53–71%), 52 (95% CI 44–61%), and 46 (95% CI 40–52%), respectively;
- for progression-free survival were 51 (95% CI 38–64%), 40 (95% CI 32–48%), 34 (95% CI 27–41%), and 27 (95% CI 23–31%), respectively;
- and for treatment-related mortality (TRM) were 18 (95% CI 14–21%), 21 (95% CI 17–25%), 20 (95% CI 13–26%), and 27 (95% CI 21–33%), respectively.
- Additionally, the pooled 100-day TRM was 12 (95% CI 5–18%).
- The incidences of grades II–IV acute graft-versus-host disease (GVHD) and chronic GVHD were 34 (95% CI 30–37%) and 51 (95% CI 46–56%), respectively. The incidences of relapse rate (RR) and death rate were 50 (95% CI 45–55%) and 51 (95% CI 45–57%), respectively.
- Importantly, disease progression was the most major cause of death (48%), followed by TRM (44%). The results failed to show an apparent benefit of allo-SCT for standard risk patients, compared with tandem auto-SCT. In contrast, all 14 trials in our study showed that patients with high cytogenetic risk after allo-SCT had similar OS and PFS compared to those with standard risk, suggesting that allo-SCT may overcome the adverse prognosis of high cytogenetic risk

Anmerkung/Fazit der Autoren

Due to the lack of consistent survival benefit, allo-SCT should not be considered as a standard of care for newly diagnosed and relapsed standard-risk MM patients. However, for patients with high-risk MM who have a poor long-term prognosis, allo-SCT may be a strong consideration in their initial course of therapy or in first relapse after chemotherapy, when the risk of disease progression may outweigh the transplant-related risks. A large number of prospective randomized controlled trials were needed to prove the benefits of these therapeutic options.

Dhakal B et al., 2018 [4].

Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: A Systematic Review and Meta-analysis.

Fragestellung

To perform a systematic review, conventional meta-analysis, and network meta-analysis of all phase 3 randomized clinical trials (RCTs) evaluating the role of HDT/ASCT.

Methodik

Population:

- Patients with newly diagnosedMMundergoingHDT/ASCT

Intervention:

- Combination chemotherapy with novel agents followed by consolidation with HDT/ASCT
- directly compared HDT1 vs HDT2 (for network meta analysis only).

Komparator:

- standard-dose therapy (SDT) alone

Endpunkte:

- PFS, OS, CR, TRM

Recherche/Suchzeitraum:

- Cochrane Central, MEDLINE, and Scopus from January 2000 through April 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs (2421 patients) for conventional meta-analysis and 5 RCTs (3171 patients) for network meta-analysis

Charakteristika der Population:

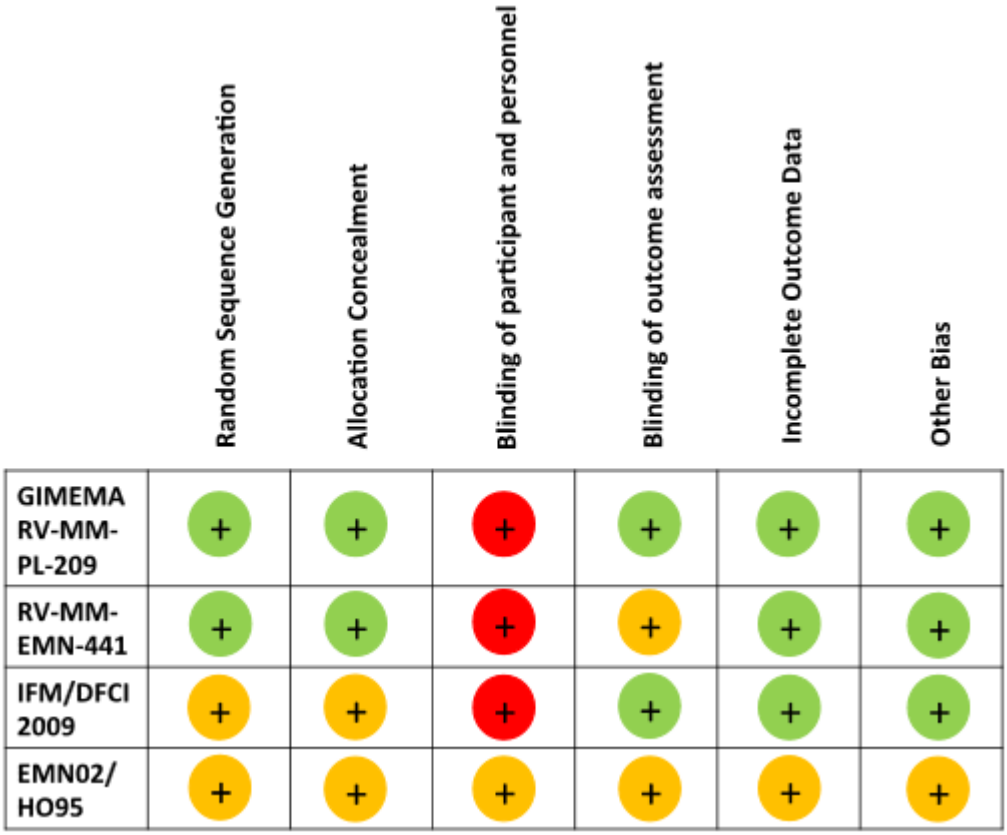
Table 1. Baseline Demographics of Relevant Randomized Clinical Trials

Source	Patients, No.	ISS III, %	High-Risk Cytogenetics, %[a]	Follow-up, mo.	Induction	Conditioning	SDT Regimen	Maintenance (HDT + SDT)
Palumbo et al,[8] 2014	273	23.6	28.8	51.2	RD	MEL 200 × 2	MPR	LEN until progression vs none
Gay et al,[7] 2015	256	29.0	21.8	52	RD	MEL 200 × 2	CRD	LEN + P vs LEN until progression
Attal et al,[5] 2015	700	18.0	12.8	44	RVD	MEL 200	RVD for 8 cycles	LEN for 1 y
Cavo et al,[6] 2016	1192	21.0	25	26	CyBorD	MEL 200 × 1 or 2	VMP for 4 cycles	LEN until progression

Abbreviations: CRD, cyclophosphamide, revlimid, and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; HDT, high-dose therapy; ISS, International Staging System; LEN, lenalidomide; LEN+P, lenalidomide plus prednisone; MEL 200, melphalan 200 mg/m^2; MPR, melphalan, prednisone, and revlimid; OS, overall survival; PFS, progression-free survival; RD, revlimid and dexamethasone; RVD, revlimid, bortezomib, and dexamethasone; SDT, standard-dose therapy; VMP, bortezomib, melphalan, and prednisone.

[a] High-risk cytogenetics include t(4:14), t(14:16), t(14:20), 17p deletion, 1q gain, and 1p deletion.

Qualität der Studien:



Studienergebnisse:

- Conventional meta-analysis:
  - The combined odds for complete response were 1.27 (95%CI, 0.97-1.65; P = .07) with HDT/ASCT when compared with SDT.
  - The combined HR for PFS was 0.55 (95%CI, 0.41-0.74; P < .001) and 0.76 for OS (95%CI, 0.42-1.36; P = .20) in favor of HDT. Meta-regression showed that longer follow-up was associated with superior PFS (HR/mo, 0.98; 95%CI, 0.96-0.99; P = .03) and OS (HR/mo, 0.90; 95%CI, 0.84-0.96; P = .002).
  - For PFS, tandem HDT/ASCT had the most favorable HR (0.49; 95%CI, 0.37-0.65) followed by single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone (HR, 0.53; 95%CI, 0.37-0.76) and single HDT/ASCT alone (HR, 0.68; 95%CI, 0.53-0.87) compared with SDT.
  - For OS, none of the HDT/ASCT-based approaches had a significant effect on survival.
  - Treatment-related mortality with HDT/ASCT was minimal (<1%).
- NMA:
  - In addition to the 4 studies included in the conventional meta-analysis, we included the results of the recent study from the Blood and Marrow Transplant Clinical Trials Network (BMTCTN0702) or STaMiNa study.10 In this study, after receiving HDT1, the patients were randomized into 3 different arms: (1) HDT2 (n = 247); (2) HDT1 plus 4 cycles of VRD (n = 254); and (3) none (N = 257). All 3 arms received lenalidomide maintenance until progression. More than 50% of the patients in all 3 arms received prior induction with

VRD; however, 32% of patients in HDT2 arm and 11% of patients in HDT1 plus VRD arm did not receive the assigned post-HDT1 treatment. The study showed no difference in the OS (HDT2, 85%; HDT1 plus VRD, 85.7%; and HDT1, 83.4%) and PFS (HDT2, 56.5%; HDT1 plus VRD, 56.7%; and HDT1, 52.2%) at 38 months follow-up.

- SDT was used as the comparator: the solid lines show the results of univariate network meta-analysis run separately for PFS and OS, and the dashed lines (and estimates in italic) show the results of the multivariate network meta-analysis that incorporates the correlation between PFS and OS "inferring" the OS results of trials that did not report OS. Treatments based on HDT/ASCT were associated with superior PFS compared with SDT. Furthermore, HDT2 had the most favorable results for PFS compared with SDT (HR, 0.49;95%CI,0.37-0.65) followed by HDT1 plus VRD(HR,0.53; 95% CI, 0.37-0.76). For OS, none of the HDT/ASCT-based approaches had a significant effect on survival compared with SDT. No significant inconsistency was found; thus, the results of the consistency model are presented. The results of the inconsistency model were not qualitatively different.
- Among the results shown, the comparison of HDT2 vs HDT1 is worth mentioning. Our results showed that HDT2 (HR, 0.79; 95% CI, 0.55-0.92; P < .001) and HDT1 plus VRD (HR, 0.78; 95% CI, 0.54-1.00; P = .02) were associated with superior PFS compared with HDT1, but no difference in OS was observed.

Anmerkung/Fazit der Autoren

Up-front HDT/ASCT remains an effective treatment strategy for patients with newly diagnosed MM and has an acceptable profile of toxic effects and costs.

Chen M et al., 2018 [3]

Immunomodulatory drugs and the risk of serious infection in multiple myeloma: systematic review and meta-analysis of randomized and observational studies.

Fragestellung

to assess the risk of serious infection at different treatment status (induction therapy, maintenance therapy, and relapse and refractory therapy) and help in guiding decisions on the treatment in patients with MM.

Methodik

Population:

- patients with MM

Intervention/Komparator:

- patients with MM initiating a new immunomodulatory therapy regimen including thalidomide, lenalidomide, or pomalidomide

Endpunkte:

- one or more adverse events about infection

Recherche/Suchzeitraum:

- Medline, Web of Science, China National Knowledge Infrastructure, and the Cochrane Central Register of Controlled Trials from inception to 20 May 2017.

Qualitätsbewertung der Studien:

- Jadad scale & GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 92 studies involving 19,876 patients
- 45 RCTs, representing 16,291 patients, and 47 cohort studies, involving 3285 patients. IMiDs used in MM included thalidomide in 55 studies, lenalidomide in 30 studies, and pomalidomide in 7 studies.

Qualität der Studien:

- Siehe Ergebnisteil

Studienergebnisse:

A total of 810 episodes of serious infection occurred in 5940 patients treated with thalidomide-based regimens and the incidence of treatment on induction (ASCT eligible), induction (non-ASCT eligible), maintenance, and relapsed or refractory were 14.80, 11.00, 10.70, and 7.00%, respectively. Fifteen trials reported overall 440 serious infection events in 5293 MM patients who used lenalidomide-based regimens for treatment. The rates of serious infection on induction, maintenance, and relapsed or refractory therapy were 12.30, 8.20, and 7.20%. There were 10 of 384 patients who received pomalidomide-based regimen therapy experiencing serious infection. Pomalidomide-based regimens were used

Table 3 Rates of serious infection in patients with MM from RCTs

IMiDs	Treatment status	Pooled incidence	95% CI	I^2	Model
Thalidomide	Induction (ASCT eligible)	14.80%	6.40–23.10%	98.20%	Random-effect
	Induction (ASCT ineligible)	11.00%	7.90–14.20%	79.5%	Random-effect
	Maintenance	10.70%	5.90–15.50%	81.90%	Random-effect
	Relapsed and refractory	7.00%	2.00–11.90%	77.20%	Random-effect
Lenalidomide	Induction (ASCT ineligible)	12.30%	9.90–14.60%	57.00%	Random-effect
	Maintenance	8.20%	4.90–11.40%	68.40%	Random-effect
	Relapsed and refractory	7.20%	3.90–10.50%	96.20%	Random-effect
Pomalidomide	Relapsed and refractory	23.00%	3.90–42.20%	94.50%	Random-effect

MM multiple myeloma, *IMiDs* immunomodulatory drugs, *CI* confidence interval

Relative risk of serious infection

- We performed meta-analysis to quantify the risk of serious infection with use of IMiD-based therapy versus conventional therapy.
- A total of 31 **RCTs** involving 11,890 patients (6087 patients used IMiDs-based therapy and 5803 patients used conventional therapy) were included in the metaanalysis.

(…) For ASCT-eligible induction treatment, 8 studies reported 318 serious infection events in 1612 patients who received IMiD-based therapy. Since all the patients only used thalidomide-based regimens for therapy…

- …when we pooled the data, patients using thalidomide-based regimens for therapy showed a significantly decrease risk for serious infection compared with the control (RR = 0.82, 95% CI 0.72–0.94, p < 0.01). Using GRADE, we rated the quality of identified studies as moderate, owing to risk of bias.
- IMiD-based maintenance therapy statistically significantly increased the rate of serious infection in patients with MM (RR = 1.59, 95% CI 1.26–2.01, p < 0.01). Using GRADE, we rated the quality of identified studies as moderate, due to risk of bias.
- Subgroup analysis showed that lenalidomide-based maintenance therapy significantly increased risk of serious infection (RR = 2.45, 95% CI 1.57–3.83, p < 0.01).
- However, thalidomide-based maintenance therapy did not show a significant increase of risk of serious infection (RR = 1.30, 95% CI 0.98–1.71, p = 0.068). We graded the results as low because of risk of bias and imprecision.

  (…)

Anmerkung/Fazit der Autoren

In conclusions, our systematic review and meta-analysis showed that the incidence and risk of serious infection were high in MM patients treated with IMiDs. Pomalidomide was associated with the highest rate of serious infection in patients with relapsed and refractory MM. So, preventive and therapeutic management are essential for MM patients receiving IMiDs.

Kommentare zum Review

- Ergebnisdarstellung fokussiert auf Ergebnissen der RCTs und SZT geeignete Patienten.

3.4 Leitlinien

NICE, 2016 [12].

National Institute for Health and Care Exellence (NICE)

Myeloma: diagnosis and management

Leitlinienorganisation/Fragestellung

This guideline covers the diagnosing and managing of myeloma (including smouldering myeloma and primary plasma cell leukaemia) in people aged 16 and over. It aims to improve care for people with myeloma by promoting the most effective tests and treatments for myeloma and its complications.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

- Anwendung von GRADE
- GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."

Recommendations

Managing newly diagnosed myeloma

- First-line treatment
  - 1.5.1 Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. [This recommendation is from Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (NICE technology appraisal guidance 311).]
  - 1.5.2 Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. [This recommendation is from Bortezomib and thalidomide for the first-line treatment of multiple myeloma (NICE technology appraisal guidance 228).]

- 1.5.3 Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
  - high-dose chemotherapy with stem cell transplantation is considered inappropriate

  and
  - the person is unable to tolerate or has contraindications to thalidomide. [This recommendation is from Bortezomib and thalidomide for the first-line treatment of multiple myeloma (NICE technology appraisal guidance 228).]

First autologous stem cell transplantation

- 1.5.4 Consider using frailty and performance status measures that include comorbidities to assess the suitability of people with myeloma for first autologous stem cell transplant.
- 1.5.5 Do not use age or the level of renal impairment alone to assess the suitability of people with myeloma for first autologous stem cell transplant.

Allogeneic stem cell transplantation

- 1.5.6 Take into account that only a small number of people with myeloma are suitable for allogeneic stem cell transplantation.
- 1.5.7 When assessing whether people with myeloma are suitable for an allogeneic stem cell transplant, take into account:
  - whether the person has chemosensitive disease
  - how many previous lines of treatment they have had
  - whether a fully human leukocyte antigen (HLA) matched donor is available
  - how graft-versus-host disease (GvHD) and other complications may get worse with age
  - the risk of higher transplant-related mortality and morbidity, versus the potential for long-term disease-free survival
  - improving outcomes with other newer treatments
  - the person's understanding of the procedure and its risks and benefits.
- 1.5.8 Consider allogeneic stem cell transplantation as part of a clinical trial if one is available.

Alberta Provincial Hematology Tumour Team, 2015 [2].

Alberta Provincial Hematology Tumour Team

Multiple Myeloma

Leitlinienorganisation/Fragestellung

(…) What are the most suitable management strategies of multiple myeloma and related disorders?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The MEDLINE (1966 through July 2012), PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases were searched. In addition, the ASCO and ASH Abstracts and Proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials.

LoE/GoR

- kein Graduierungssystem (Formulierungen im Text)

Recommendations

Treatment Guidelines for Newly Diagnosed Multiple Myeloma

- Patients ≤ 65 Years Old and Transplant-Eligible: Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, patients who are 65 years old or younger and are transplant-eligible should receive a course of therapy consisting of:
  - Pre-transplant induction with a 3-drug regimen that includes a novel agent
  - High dose melphalan +/- bortezomib followed by autologous stem cell transplantation
  - Post transplant consolidation
  - Maintenance lenalidomide and/or bortezomib until disease progression.

Induction Regimens:

- Induction regimens should contain at least one novel agent (e.g. bortezomib, lenalidomide, thalidomide). There is consensus amongst the myeloma physicians that a triple drug based induction regimen results in superior outcomes with improved rate and depth of responses (higher CR and sCR rates). Four randomized trials comparing doublet versus triplet-based regimen are in favor of triplet-based regimen since the latter results in improved responses as well as progression free survival.20-25

Referenzen aus Leitlinie:
20. Gertz MA, Lacy MQ, Dispenzieri A, Greipp PR, Litzow MR, Henderson KJ, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and −17p13 in myeloma patients treated with high-dose therapy. Blood 2005 Oct;106(8):2837-40.
21. Paiva B, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation BLOOD, 15 NOVEMBER 2008 VOLUME 112, NUMBER 10. 4017-2023
22. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075-2085.
23. Cavo M et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012 Jul 5;120(1):9-19.
24. Rosinol L et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM studyBlood. 2012;120(8): 1589-1596
25. Garderet L et al. Superiority of the Triple Combination of Bortezomib-Thalidomide-Dexamethasone Over the Dual Combination of Thalidomide-Dexamethasone in Patients With Multiple Myeloma Progressing or Relapsing After Autologous Transplantation: The MMVAR/IFM 2005-04 Randomized Phase III Trial From the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation J Clin Oncol. 2012 Jul 10;30(20):2475-2482

Bortezomib-based induction regimens:

- Numerous studies have shown that the depth of response achieved following ASCT is predictive of outcome. Patients achieving CR, nCR, and/or VGPR after transplantation have longer remissions and survival times than those with lesser responses. It has been suggested that if induction regimens with higher initial response rates were used prior to transplant, this should produce deeper responses post transplant, resulting in better PFS and OS. Until recently, this potential benefit of more effective induction had not been shown. A large meta-analysis failed to demonstrate any survival advantage for combination chemotherapy (i.e. VAD, VBMCP) compared to melphalan + prednisone.33

Referenzen aus Leitlinie:
33. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998 Dec;16(12):3832-42.

- A randomized trial comparing induction with TD versus VAD showed higher response rates to TD induction, but similar response rates (VGPR 42% vs 44%) after transplant. However, recent studies of bortezomib based regimens suggest the choice of induction regimen may indeed affect outcome post transplant33-36. They showed an improvement in response with higher CR/near CR post-transplant, and superior progression free survival for those receiving bortezomib based regimens, with an improvement in overall survival seen in one study. 33-36

Referenzen aus Leitlinie:
33. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. J Clin Oncol 1998 Dec;16(12):3832-42.
34. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010;28:4621-4629.
35. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial. J Clin Oncol 2012 Aug 20;30(24):2946-2955.
36. Rosiñol L, Oriol A, Teruel AI, et al: .Superiority of bortezomib, thalidomide and dexamethasone (VTD) as induction pre-transplantation therapy in multiple myeloma: a randomized phase III PETHEMA/GEM study. Blood. 2012 Jul 12.

- Bortezomib and dexamethasone based regimens for 3-4 cycles are well tolerated and shown to be more effective than older regimens, improving response rate, PFS, and OS post transplant. Bortezomib and dexamethasone should be included as part of multi-drug regimens as standard induction therapy prior to stem cell transplantation, along with a third agent such as cyclophosphamide (CyBorD31) and lenalidomide* (VRD37). (…)

Referenzen aus Leitlinie:
31. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009;23(7):1337-1341
37. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116(5):679-686.

CYBORD:

Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days. Each cycle consists of:

- Cyclophosphamide 300mg/m2 orally weekly for 4 weeks
- Bortezomib 1.5mg/m2 intravenously or subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

A twice-weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy.

VRD*:

Patients should receive no more than 4 cycles prior to attempted stem cell mobilization. Cycles are repeated every 28 days. Each cycle consists of:

- Lenalidomide 25mg orally daily for 21 days
- Bortezomib 1.5mg/m2 subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

A 21-day schedule can be used for sicker patients requiring a more rapid initial response to therapy:

- Lenalidomide 25mg orally daily for 14 days
- Bortezomib 1.3mg/m2 subcutaneously twice weekly for 2 weeks
- Dexamethasone 40mg orally twice weekly for 2 weeks.

Thalidomide-based regimens:

- Several large randomized trials have compared induction therapy with thalidomide to dexamethasone.38-46. In patients eligible for SCT, a thalidomide-based induction regimen resulted in a significantly higher response rate (CR and VGPR) and PFS/TTP/EFS. The impact on OS of induction therapy with thalidomide followed by autologous stem cell transplant remains a matter of debate. Only one study did demonstrate an overall survival advantage with thalidomide –VADoxil38. Randomized controlled trials of thalidomide have demonstrated higher incidence of adverse events with thalidomide as compared to standard therapy. In particular, VTE, peripheral neuropathy, & constipation are increased. Risk of VTE (between 4 and 20%) is greater when thalidomide is combined with steroid &/or chemo but less when thalidomide used as maintenance

Referenzen aus Leitlinie:
38. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR, Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006 Jan;24(3):431-6.
39. Rajkumar SV, Rosinol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 2008 May;26(13):2171-7.
40. Ludwig H, Hajek R, Tothova E, Drach J, Adam Z, Labar B, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 2009 Apr;113(15):3435-42.
41. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood 2005 Jul;106(1):35-9.
42. Macro M, Divine M, Uzunhan Y, Jaccard A, Bouscary D, Leblond V, et al. Dexamethasone + thalidomide (Dex/Thal) compared to VAD as a pre-transplant treatment in newly diagnosed multiple myeloma (MM): a randomized trial [abstract]. Blood 2006;108(11 Part 1):22.
43. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, van der Holt B, Martin H, Barge R, et al.Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. Haematologica 2008 Jan;93(1):124- 7.
44. Zamagni E, Valdre L, Cini M, Legnani C, Tosi P, Tacchetti P, et al. Baseline Thrombophilic alterations and risk of venous thromboembolism in 266 multiple myeloma patients primarily treated with thalidomide and high-dose dexamethasone [abstract]. Blood 2007;110(11).
45. Zervas K, Dimopoulos MA, Hatzicharissi E, Anagnostopoulos A, Papaioannou M, Mitsouli C, et al. Primary treatment of multiple myeloma with thalidomide, vincristine, liposomal doxorubicin and dexamethasone (T-VAD doxil): a phase II multicenter study. Ann Oncol 2004 Jan;15(1):134-8.
46. Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999 Jan;93(1):55-65.

Lenalidomide-based induction regimen:

- The combination of lenalidomide and dexamethasone is a well tolerated and convenient oral regimen resulting in high response rates when followed by ASCT, with 3 year PFS and OS

of 64% and 94% respectively47. Two large randomized trials comparing an induction therapy with a lenalidomide-based regimen have reported high rates of CR/VGPR and high 2-year PFS and OS rates.48,49. Lenalidomide with low-dose dexamethasone (40 mg PO weekly) (Ld) is superior to lenalidomide with standard-dose dexamethasone (LD) (40 mg PO days 1-4, 9-12, 17-20). The impact of a lenalidomide-based induction regimen on survival post-ASCT is unclear since transplant is often deferred until relapse in these studies. Patients treated with 4 cycles of lenalidomide followed by ASCT had a 2 year OS of 93%, similar to those treated with Ld until disease progression.

Because prolonged therapy with lenalidomide can impair stem cell mobilization, consider stem cell collection within 4 cycles of induction lenalidomide.

Referenzen aus Leitlinie:
47. Siegel DS, Jacobus S, Rajkumar VS, et al. Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in the ECOG E4A03 randomized clinical trial [Abstract]. Blood. 2010;116:38.
48. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010 Jan;11(1):29-37
49. Zonder JA, Crowley J, Hussein-Bolejack V, Moore DF, Whittenberger BF, Abidi MH, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): results of the randomized, double-blinded, placebo-controlled SWOG trial S0232 [abstract]. Blood 2007;110(11):32a.

Other Regimens:

- Single agent dexamethasone is associated with suboptimal response and should not be used as the only therapy for myeloma. The VAD regimen should not be used due to the toxicity of this regimen (neurotoxicity, cardiac toxicity, myelosuppression) and its inferior outcomes compared to bortezomib containing regimens.

2. Stem Cell Transplantation:

- Autologous Stem Cell Transplant (ASCT):

Four large randomized trials have demonstrated the superiority of autologous stem cell transplantation to standard dose chemotherapy with significant prolongation of TTP and OS.50-53 Other trials, with several caveats have failed to demonstrate the same benefit from ASCT.54-57 Patients are considered transplant eligible if they are under the age of 65, meet minimal requirements for underlying organ function and all other transplant eligibility requirements of the Calgary or Edmonton transplant programs. There is no proven benefit to transplant over standard therapy for patients over the age of 65. These patients can be considered for ASCT if they are meet all transplant eligibility criteria, are physiologically very fit, and have no significant comorbid illnesses.

Transplant eligible patients should receive 3-4 cycles of induction therapy before proceeding to ASCT. The achievement of CR is not required to proceed to transplant. Patients who fail to achieve CR after 3-4 cycles of induction, including those with primary refractory disease, can still benefit from high dose therapy and ASCT and should still be referred for transplant evaluation. Patients with renal failure on dialysis are candidates for autologous stem cell transplant and should be referred without significant delays for transplant evaluation. Twenty to twenty-five percent of patients do recover their renal function and become dialysis-independent up to 6 months post-transplant.

Referenzen aus Leitlinie:
50. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiplemyeloma. Intergroupe Francais du Myelome.NEnglJ Med 1996;335(2):91-7.

51. Morgan GJ, Davies FE, Hawkins K, Brown J, Bell SE, Drayson MT, et al. The MRC Myeloma VII Trial of standard versus intensive treatment in patients <65 years of age with multiple myeloma [abstract]. Blood 2002;100: 178a. Abstract 668.
52. Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, et al. Intermediate dose melphalan improves survival of myeloma patients aged 50 to 70 : results of a randomized phase 3 study. Blood 2004 Nov;104(10):3052-7.
53. Palumbo A, Cavallo F, Gay F, etal. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. N Engl J Med 2014; 371:895-905September 4, 2014DOI: 10.1056/NEJMoa1402888
54. Fermand JP, Katsahian S, Devine M, Leblond V, Dreyfus F, Macro M, et al. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005 Dec;23(36):9227-33.
55. Bladé J, Sureda A, Ribera JM, Diaz-Mediavilla J, Palomera L, Fernandez-Calvo J, et al. High-dose therapy autotransplantation/intensification vs. continued conventional chemotherapy in multiple myeloma patients responding to initial treatment chemotherapy. Results of a prospective randomized trial from the Spanish Cooperative Group PETHEMA [abstract]. Blood 2001;98:815a. Abstract 3386.
56. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006 Feb;24(6):929-36.
57. Segeren CM, Sonneveld P, van der Holt B, Vellenga E, Croockewit AJ, Verhoef GE, et al. Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. Blood 2003 Mar;101(6):2144-51.

Four studies have been conducted to date comparing tandem autologous to tandem autologous-allogeneic stem cell transplant. In a French study trial (IFM99-03) of high risk patients (del13 and high β2), no difference in outcome was seen between the two approaches. However it should be noted that only patients with high risk disease were enrolled into this study and high dose ATG was used in the conditioning regimen.65 In a study by Bruno and colleagues, allogeneic transplant was by far superior however in this study the results of the tandem autologous arm were lower than expected and the study had several reporting caveats.66 Early results from the PETHEMA group suggest superior results with allogeneic transplant; however they only report a trend for better PFS, not OS.68The largest study comparing autologous to transplantation was performed by the US Blood and Marrow Clinical Trials Network. 625 patients were biologically assigned to receive either a tandem ASCT with melphalan 200 mg/m2 (n = 436) or ASCT with melphalan 200 mg/m2 followed by an allogeneic SCT conditioned with fludarabine and 200 cGy of total body irradiation (n = 189). The 3-year PFS was 46% for the tandem autologous arm versus 43% for the autologous-allogeneic arm (*P* = .67). OS at 3 years was also not significantly different between the groups: 80% for the tandem autografts versus 77% for the autologous-allogeneic arm. Assignment to the autologous-allogeneic arm was associated with worsened survival in patients with stage I and II disease, but not in those with stage III disease68. At this point, allogeneic transplant is not considered a standard part of therapy for newly diagnosed or relapsed myeloma and should be performed only in the setting of a clinical trial.

Referenzen aus Leitlinie:
65. Garban F, Attal M, Michallet M, Hulin C, Bourhis JH, YakoubAgha I, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006 May;107(9):3474-80.
66. Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007 Mar;356(11):1110-20.
68. Krishnan A, Pasquini MC, Logan B, et al: Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol. 2011 Dec;12(13):1195-203.

3. Post-Transplant Therapy:

- Consolidation:

All patients should receive 2 cycles of consolidation therapy in addition to maintenance therapy. Both bortezomib23 and lenalidomide69 based regimens have been used. Compared to thalidomide and dexamethasone, the combination of bortezomib, thalidomide, and dexamethasone as consolidation after ASCT significantly improved CR (46% vs 60%) and

CR/nCR rates (61% vs 73%). With a median follow-up of 30.4 months from start of consolidation, 3-year progression-free survival was significantly longer for the VTD group (60% vs 48% for TD). Grade 2 or 3 peripheral neuropathy (8.1% vs 2.4%) was more frequent with VTD (grade 3, 0.6%) versus TD consolidation.

Our recommendation is for 2 cycles of consolidation with VRD* in all patients post ASCT. Lenolidomide in place of thalidomide should be used to minimize risk of neuropathy.

- Bortezomib 1.3 mg/m2 on days 1, 8, 15, and 22
- Lenaldomide 10mg/d, days 1-21/28 (or Thalidomide 100 mg daily)
- Dexamethasone 40 mg on days 1, 8, 15, 22

Referenzen aus Leitlinie:
23. Cavo M et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012 Jul 5;120(1):9-19.
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Maintenance Therapy:

- Lenalidomide:

Two phase III trials have examined the role of lenalidomide maintenance following ASCT. The CALGB 100104 (n=460) trial compared a strategy of maintenance with lenalidomide (10mg daily) to placebo following ASCT69.At a median follow up of 34 months, maintenance resulted in an improved TTP of 46 months versus 27 months for placebos (p<0.001). Overall survival was also improved, with HR for death 0.62 (p<0.03). Lenalidomide maintenance was associated with an increase in second primary malignancies (SPM) (7.8% vs 2.6%). However event free survival analysis including SPM as study related events continued to show improved survival outcomes in favor of the maintenance arm.

The IFM 2005-02 trial70 randomized 614 patients to maintenance with lenalidomide 10-15mg daily following ASCT. All patients received two cycles of consolidation with lenalidomide 25mg daily for 21 of 28 days prior to starting maintenance. With a median follow up of 45 months, the 4 year PFS was 43% for lenalidomide compared to 22% for placebo (p<0.001). There was no difference in OS (73% vs 75%). There were 23 second primary malignancies in the lenalidomide group and 9 in the placebo group.

A retrospective analysis of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma including 3846 patients reported an incidence rate of second primary malignancies (SPMs) of 3.6271. Incidence rate of invasive (hematologic and solid tumor) SPMs was 2.08, consistent with the background incidence of developing cancer. In a separate analysis of pooled data from pivotal phase 3 trials of relapsed or refractory MM (n = 703), the overall IR of SPMs was 3.98 (2.51-6.31) with lenalidomide/dexamethasone and 1.38 (0.44-4.27) with placebo/dexamethasone. IRs of non-melanoma skin cancers were 2.40 (1.33-4.33) and 0.91 (0.23-3.66), respectively. IRs of invasive SPMs were 1.71 (0.86-3.43) and 0.91 (0.23-3.66), respectively.

Referenzen aus Leitlinie:
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71. Dimopoulos MA, Richardson PG, Brandenburg N, et al: A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood. 2012 Mar 22;119(12):2764-7

- Bortezomib:

The phase III HOVON-65/ GMMG-HD4 trial randomized 827 patients to receive VAD induction followed by ASCT and maintenance therapy with thalidomide (arm A) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by ASCT and maintenance with bortezomib every 2 weeks for 2 years (arm B)22. The strategy of bortezomib-based induction with bortezomib maintenance resulted in superior response rates (≥ VGPR 76% vs 56%, p<0.001) and PFS (35 vs 28 months, p=0.02). The study was not designed to evaluate the benefit of bortezomib maintenance on its own. However, the number of patients achieving a response upgrade after starting maintenance was similar between the thalidomide and bortezomib maintenance arms suggesting similar effects of these two strategies. An analysis of PFS calculated from the time of last HDM showed a significant difference in favor of the bortezomib arm (31 versus 26 months). This indicates that although post-transplantation bortezomib and thalidomide both achieved similar response upgrades, bortezomib contributed more to improvement of PFS. Importantly in this study, for patients with del17p, PAD followed by bortezomib maintenance significantly improved PFS (mPFS in arm B vs arm A: 26.2 vs 12.0 months; *P*=.024) and overall survival (3-year OS rate in arm B vs arm A: 69% vs 17% *P*=.028)

Referenzen aus Leitlinie:
22. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075-2085.

- Thalidomide:

Thalidomide maintenance has consistently been associated with an improvement in PFS with a variable effect on OS. However it does lead to reduction in quality of life, and is frequently discontinued due to side effects and toxicity. Four large randomized trials have reported an improvement in TTP and OS with the use of thalidomide maintenance.72-75 The four trials used different doses (100-400 mg) of thalidomide as well as different durations of therapy (6-48 months). The median duration of therapy in the IFM99-02 study was approximately 18 months, with a median thalidomide dose of 200 mg. The IFM99-02 trial compared no maintenance (arm A), maintenance pamidronate (arm C) or maintenance thalidomide (<400 mg) + pamidronate (arm B), 2 months post-tandem autologous transplant in myeloma patients with only one risk factor (β2 microglobulin >3 mg/L or del13).72

  - Maintenance thalidomide improved response rate (higher CR and VGPR rate with thalidomide: 55% arm A, 57% arm B, 67% arm C)
  - Thalidomide improved 3-year EFS: 36% arm A, 37% arm B and 52% arm C
  - Thalidomide improved 4-year OS: 77% arm A, 74% arm B, 87% arm C
  - Pamidronate did not decrease the incidence of bone events
  - Patients with del13 or those who achieved a VGPR or better did not benefit from thalidomide

Referenzen aus Leitlinie:
72. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006 Nov;108(10):3289-94.
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74. Zangari M, van Rhee F, Anaissie E, Pineda-Roman M, Haessler J, Crowley J, Barlogie B. Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1. Br J Haematol 2008;141:433-44.
75. Cavo M, Di Raimondo F, Zamagni E, Patriarca F, Tacchetti P, Casulli AF, et al. Short-term thalidomide incorporated into double autologous stem-cell transplantation improves outcomes in comparison with double autotransplantation for multiple myeloma. J Clin Oncol 2009 Oct;27(30):5001-7.

- α-Interferon (IFN):

Clinical trials of IFN maintenance produce conflicting results. However it has considerable toxicity and very poor tolerance. With the availability of better tolerated, more effective therapies, the use of IFN is not recommended.39, 56, 76, 77

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39. Rajkumar SV, Rosinol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 2008 May;26(13):2171-7.
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76. Cunningham D, Powles R, Malpas J, Raje N, Milan S, Viner C, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. Br J Haematol 1998 Jul;102(2):495-502.
77. Bjorkstrand B, Svensson H, Goldschmidt H, Ljungman P, Apperley J, Mandelli F, et al. Alpha-interferon maintenance treatment is associated with improved survival after high-dose treatment and autologous stem cell transplantation in patients with multiple myeloma: a retrospective registry study from the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transpl 2001;27(5):511-5.

Prednisone:

In non-transplant patients, one randomized study by Berenson and the SWOG group showed better EFS (14 vs. 5 months; p=0.03) and OS (37 vs. 26 months; p=0.05) with prednisone 50 mg compared to prednisone 10 mg.78 Prednisone is not recommended for maintenance following ASCT.

Members of the Alberta Provincial Hematology Tumour Board recommend maintenance therapy with lenalidomide or bortezomib for patients without progressive disease following ASCT. The risk of SPMs must be taken into account before initiating lenalidomide treatment. In the context of the observed progression free survival benefit after ASCT, the benefit/risk profile of lenalidomide/dexamethasone remains positive. Maintenance with bortezomib (with or without lenalidomide) should be considered in patients with del17p.

Referenzen aus Leitlinie:

78. Berenson JR, Crowley JJ, Grogan TM, Zangmeister J, Briggs AD, Mills GM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. Blood 2002;99(9):3163-8.

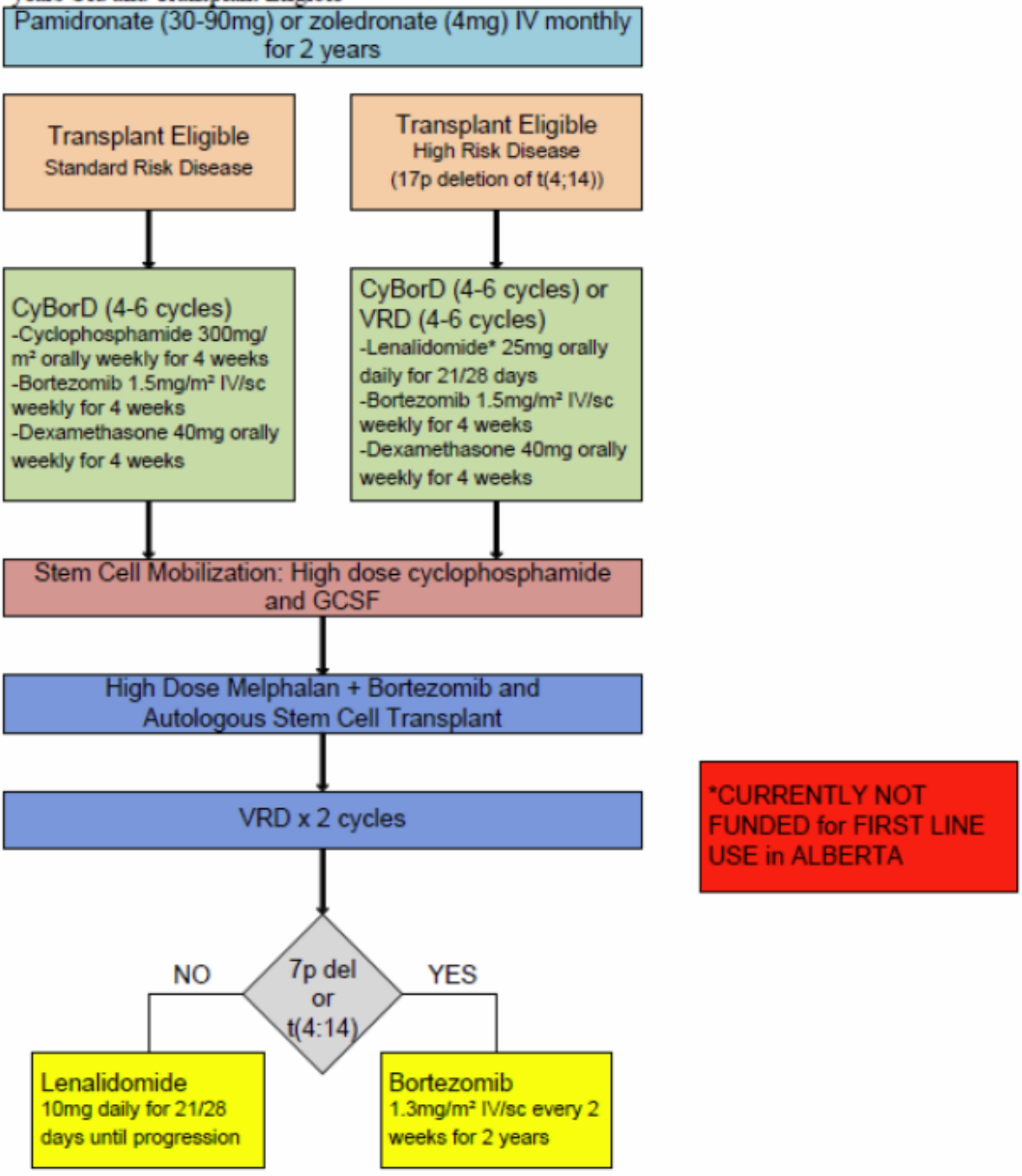
Summary:

Regimens containing bortezomib and dexamethasone as well as a third agent (cyclophosphamide, lenalidomide) are the standard induction regimen prior to stem cell transplantation for transplant eligible patients with standard risk or high risk myeloma requiring treatment. VAD or single agent dexamethasone should not be used.

- CYBORD is the recommended regimen for initial therapy of newly diagnosed transplant eligible patients. Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days. A twice weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy.
- High risk patients (17p deletion, t(4;14)) should receive a bortezomib based regimen and should be considered for initial therapy with a combination of bortezomib, lenalidomide and dexamethasone (VRD)*. **Lenalidomide is not currently funded for up front treatment of myeloma.**
- Patients refractory to VCD (fail to achieve at least PR) should be switched to second line therapy with lenalidomide and dexamethasone or VRD (bortezomib days 1,4,8,11, Lenalidomide days 1-14, weekly dexamethasone) for several cycles prior to stem cell mobilization

- Cyclophosphamide 2.5g/m2 followed by growth factor administration is used for stem cell collection
- The standard stem cell transplant regimen consists of a single transplant conditioned with high dose (200mg/m2) Melphalan with bortezomib (1.3mg/m2 day -5, -2, +1, and +4)
- Following transplant: o All patients should receive 2 cycles of VRD*
  - o Following consolidation, patients with 17p deletion or t(4:14) should receive bortezomib (1.3mg/m2) every 2 weeks for 2 years. All others should receive lenalidomide 10mg daily for 21-28/28 days every 4 weeks until disease progression

Figure 1. Summary of Treatment Recommendations in Multiple Myeloma Patients ≤65 years Old and Transplant Eligible



Moreau P et al., 2017 [11].

European Society for Medical Oncology (ESMO)

Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

Treatment recommendations for MM.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,. . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [49].

- Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

Recommendations

Younger patients (<65 years or fit patients <70 years in good clinical condition).

- For patients in good clinical condition (e.g. fit patients), induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment [II, B].
- Two recent phase III trials comparing front-line ASCT versus ASCT at the time of first relapse showed that PFS was improved in the front-line ASCT arm (in the context of triplet novel agent-based induction). Response rates to induction therapy have been significantly increased by the use of novel agent-based combinations. Bortezomib dexamethasone, which is superior to the classical VAD regimen (vincristine, doxorubicin and high-dose dexamethasone) [II, B], has become the backbone of induction therapy before ASCT.
- The addition of a third agent to bortezomib dexamethasone, e.g. thalidomide (VTD), doxorubicin (PAD), lenalidomide (RVD) or cyclophosphamide (VCD), has shown higher

response rates in phase II trials. Three prospective studies have already shown that VTD is superior to thalidomide dexamethasone (TD) or bortezomib-dexamethasone [I, A].

- Two trials have prospectively compared VCD versus PAD [II, B] , and VTD versus VCD [II, B]. The first one showed that VCD and PAD were equally effective in terms of response, and that VCD was less toxic. The second one showed that VTD is the more effective regimen compared with VCD in terms of very good partial response rates, but was associated with a higher rate of peripheral neuropathy. Based on response rates, depth of response and PFS as surrogate markers for outcome, three-drug combinations including at least bortezomib and dexamethasone are currently the standard of care before ASCT. In Europe, VTD and VCD are the most preferred regimens. RVD, when approved, will probably be widely used [20]. Carfilzomiblenalidomide and dexamethasone (KRd), currently being evaluated in ongoing phase III trials, is associated with high response rates, but is currently only approved for treatment of relapsed MM.
- Four to six courses of induction are recommended before proceeding to stem cell collection.
- Melphalan [200 mg/m2 intravenous (i.v.)] is the standard preparative regimen before ASCT [II, B]. Peripheral blood progenitor cells are the preferred source of stem cells, rather than BM [III, B].
- Tandem ASCT was evaluated before the era of novel agents.
- The benefit of tandem ASCT was observed in patients not achieving very good partial response after the first ASCT. In a recent study from The Netherlands and Germany (HOVON-65/GMMG-HD4 trial), in the context of bortezomib induction and maintenance treatment, OS was better in the GMMG group (tandem ASCT) in contrast to the HOVON group (single ASCT). Nevertheless, the trial was not powered to compare single versus double ASCT. The recent EMN02/H095 trial compared single versus tandem ASCT upfront; PFS was improved in the tandem ASCT arm of the study, hampered by a short follow-up. Additional data from a similar trial (BMT CTN 0702, NCT01109004) being conducted in the USA will solve this important issue.
- Allogeneic SCT is not indicated as part of front-line therapy and should only be carried out in the context of a clinical trial.

Consolidation:

- Several trials have shown that consolidation is improving the depth of response. However, in the era of novel agent-based induction therapy, there is still not enough evidence that consolidation therapy should be systematically applied. Ongoing trials will clarify the impact of consolidation, especially in the setting of front-line ASCT, such as the EMN02/H095 and BMT CTN 0702 studies.

Maintenance

- In elderly patients following induction, several randomised trials have explored the benefit of maintenance therapy in terms of OS using either immunomodulatory drugs (IMiDs) or bortezomib: MP or a reduced-dose regimen of CTD (CTDa) with or without thalidomide maintenance, MP versus MPR versus MPR-R [17], VMPT-VT versus VMP, VMP versus VTP followed by either VP or VT maintenance. These trials have not demonstrated a clear benefit in OS, and the drugs are not yet approved by the EMA; therefore, systematic maintenance therapy currently cannot be recommended in elderly patients.

- In young patients following ASCT, phase III randomised trials have demonstrated that maintenance therapy with IMiDs, either thalidomide or lenalidomide, prolongs PFS [I, A]. A recent meta-analysis based on individual patient data of more than 1200 cases demonstrated that lenalidomide maintenance following ASCT is associated with an overall OS benefit of more than two years [I, A]. In February 2017, the EMA approved lenalidomide as monotherapy for the maintenance treatment of adult patients with newly diagnosed MM who have undergone ASCT. Bortezomib maintenance was also evaluated during a two-year study and was associated with a survival benefit over thalidomide maintenance, but induction was not identical in the two arms of this prospective trial. Bortezomib and thalidomide are not approved in this setting.

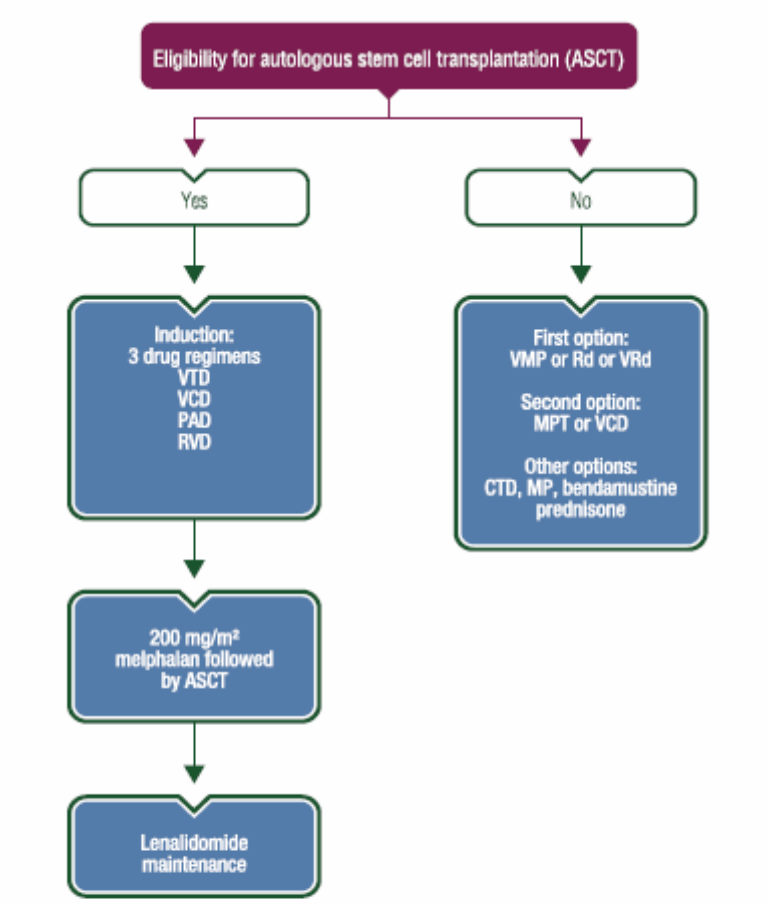


Figure 1. Front-line treatment of symptomatic multiple myeloma outside clinical trials.
CTD, cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; PAD, bortezomib, doxorubicin, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisone; VRd, lenalidomide, low-dose dexamethasone, bortezomib; VTD, bortezomib, thalidomide, dexamethasone.

Mikhael J et al., 2019 [10].

Treatment of multiple myeloma: ASCO and CCO Joint Clinical Practice Guideline

Leitlinienorganisation/Fragestellung

To provide evidence-based recommendations on the treatment of multiple myeloma to practicing physicians and others.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- from 2005 through 2018

LoE/GoR

- Strength of evidence: The quality of the total body of evidence used to inform a given recommendation is assessed to evaluate its validity, reliability, and consistency. This assessment considersthe individual study quality ratings, the overall risk of bias, and the overall validity and reliability of the total body of evidence. The summary rating is an indication of theExpertPanel's confidencein the available evidence.
- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment is primarily based on the strength of the available evidence for each recommendation and it is an indicationof theExpertPanel's confidence in its guidance or recommendation. However, where evidence is lacking, it also affords panels the opportunity to comment on the strength of their conviction and uniformity of their agreement that the recommendation represents the best possible current guidance.

Recommendations

Transplant Eligible

- Recommendation 1.1. Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 1.2. Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.1. The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids is advised prior to stem-cell collection (Type:

evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

- Recommendation 2.2. Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 2.3. Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drug exposure (more than four cycles), should be avoided in patients who are potential candidates for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.4. Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.5. The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy—patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.6. High-dose melphalan is the recommended conditioning regimen for ASCT (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 2.7. Tandem ASCT should not be routinely recommended (Type: evidence based; Evidence quality: intermediate, benefit equals harm; Strength of recommendation: strong).
- Recommendation 2.8. Salvage or delayed SCT may be used as consolidation at first relapse for those not choosing to proceed to transplant initially (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 2.9. Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).
- Recommendation 3.1. Consolidation therapy is not routinely recommended but may be considered in the context of a clinical trial. For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 3.2. Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 3.3. For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

- Recommendation 3.4. For high-risk patients, maintenance therapy with a PI with or without lenalidomide may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 3.5. There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including minimal residual disease (MRD) status (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 4.1. The quality and depth of response should be assessed by International Myeloma Working Group (IMWG) criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 4.2. The goal of initial therapy for transplant-eligible patients should be achievement of the best depth of remission. MRD-negative status has been associated with improved outcomes, but it should not be used to guide treatment goals outside the context of a clinical trial (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 4.3. It is recommended that depth of response be assessed with each cycle. Frequency of assessment once best response is attained or on maintenance therapy may be assessed less frequently but at minimum every 3 months (Type: evidence based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).
- Recommendation 4.4. Whole-body low-dose computed tomography (CT) scan has been shown to be superior to skeletal survey done with plain x-rays and is the preferred method for baseline and routine bone surveillance. Fluorodeoxyglucose positron emission tomography/CT and/or magnetic resonance imaging may be used as alternatives at baseline. They may also be used in select situations (eg, risk-stratifying smoldering myeloma, for monitoring response of nonsecretory and oligosecretory myeloma, and if CT or skeletal survey is inconclusive) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, March 2019) am 15.05.2019

#	Suchfrage
1	[mh “Multiple Myeloma”]
2	(multiple OR plasma NEXT cell):ti,ab,kw
3	(myeloma OR myelomas):ti,ab,kw
4	#2 AND #3
5	(Kahler NEXT disease* OR myelomatosis OR myelomatoses):ti,ab,kw
6	{OR #1, #4-#5}
7	#6 with Cochrane Library publication date from May 2014 to present

Systematic Reviews in Medline (PubMed) am 15.05.2019

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[tiab]) OR Plasma-Cell[tiab]) OR "Plasma Cell"[tiab]
3	(myeloma[tiab]) OR myelomas[tiab]
4	#2 AND #3
5	(("Kahler Disease*"[tiab]) OR myelomatosis[tiab]) OR myelomatoses[tiab]
6	#1 OR #4 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR

	(clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2014/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 15.05.2019

#	Suchfrage
1	Multiple Myeloma[mh]
2	((multiple[tiab]) OR Plasma-Cell[tiab]) OR "Plasma Cell"[tiab]
3	(myeloma[tiab]) OR myelomas[tiab]
4	#2 AND #3
5	(("Kahler Disease*"[tiab]) OR myelomatosis[tiab]) OR myelomatoses[tiab]
6	#1 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
8	(((#7) AND ("2014/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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