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-097 Daratumumab

Stand: Juni 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Daratumumab + Lenalidomid + Dexamethason zur Behandlung des neu diagnostizierten multiplen Myeloms; Patienten, die für eine autologe Stammzelltransplantation NICHT 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.	*Nicht angezeigt.*
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): – Daratumumab in Kombination Bortezomib, Melphalan und Prednison, Beschluss vom 21.03.2019
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 Lenalidomid und Dexamethason oder Bortezomib, Melphalan und Prednison für die Behandlung erwachsener Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzell-transplantation nicht geeignet sind.
Chemotherapien	
Bendamustin L01AA09 Bendamustin Kabi	Primärtherapie bei multiplem Myelom (Durie-Salmon-Stadium II mit Progression oder Stadium III) in Kombination mit Prednison, bei Patienten im Alter über 65 Jahren, bei denen eine autologe Stammzelltransplantation nicht in Frage kommt und die zum Zeitpunkt der Diagnose eine klinische Neuropathie aufweisen, die die Anwendung von Thalidomid oder Bortezomib-haltigen Regimen ausschließt.
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 Melphalan und Prednison für die Behandlung erwachsener Patienten mit bisher unbehandeltem multiplen Myelom indiziert, die für eine Hochdosis-Chemotherapie mit hämatopoetischer Stammzelltransplantation nicht geeignet sind. […]

Daratumumab L01XC24 Darzalex®	DARZALEX ist indiziert: • in Kombination mit Bortezomib, Melphalan und Prednison für die Behandlung erwachsener Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzelltransplantation nicht 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. Revlimid als Kombinationstherapie mit Dexamethason, oder Bortezomib und Dexamethason, oder Melphalan und Prednison ist indiziert für die Behandlung von erwachsenen Patienten mit unbehandeltem multiplem Myelom, die nicht transplantierbar sind. […]
Thalidomid L04AX02 Thalidomide Celgene	Thalidomide Celgene in Kombination mit Melphalan und Prednison ist indiziert für die Erstlinienbehandlung von Patienten mit unbehandeltem multiplen Myelom ab einem Alter von ≥ 65 Jahren bzw. Patienten, für die eine hochdosierte Chemotherapie nicht in Frage kommt.
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-097 (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

Indikation lt. Beratungsanforderung: Daratumumab in Kombination mit Lenalidomid und Dexamethason oder Bortezomib, Melphalan und Prednison für die Behandlung erwachsener Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzell-transplantation nicht geeignet sind.

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

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *multiples 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 12 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

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3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Daratumumab (neues Anwendungsgebiet: neu diagnostiziertes Multiples Myelom) vom 22. März 2019.

Anwendungsgebiet

DARZALEX ist indiziert in Kombination mit Bortezomib, Melphalan und Prednison für die Behandlung erwachsener Patienten mit neu diagnostiziertem multiplen Myelom, die für eine autologe Stammzelltransplantation nicht geeignet sind.

Zweckmäßige Vergleichstherapie

Eine Kombinationstherapie nach Maßgabe des Arztes.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Daratumumab in Kombination mit Bortezomib, Melphalan und Prednison gegenüber einer Kombinationstherapie nach Maßgabe des Arztes: Anhaltspunkt für einen beträchtlichen Zusatznutzen.

3.2 Cochrane Reviews

Scott K et al., 2016 [11].

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

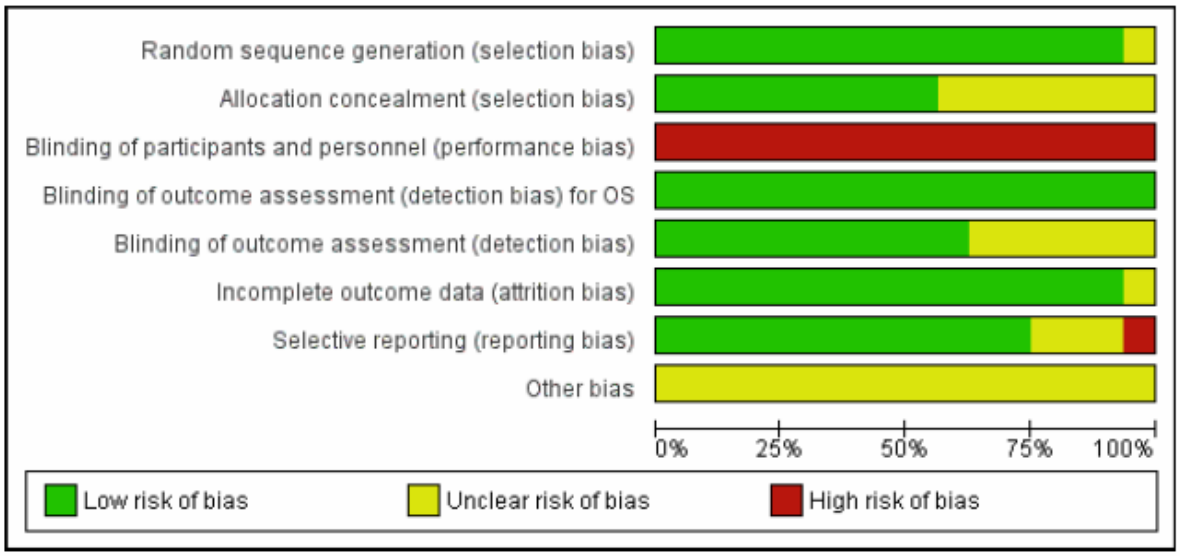
Ergebnisse

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 Fet 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 [6].

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.

Charakteristika der Population:

-

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 Xet al., 2015 [7].

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.

Weisel et al., 2017 [12].

A systematic literature review and network meta-analysis of treatments for patients with untreated multiple myeloma not eligible for stem cell transplantation

Fragestellung

to evaluate the relative efficacy of Rd versus other regimens on survival endpoints in previously untreated MM patients ineligible for ASCT.

Methodik

Population:

- adult MM patients aged 65 years or older or not eligible for stem cell transplantation

Intervention:

- lenalidomide, thalidomide, bortezomib, bendamustine, or interferon, as monotherapy or part of a combination therapy, or MP combination treatment

Komparator:

- placebo, any of the above-listed interventions at a different dose or duration, or any other active drug provided as monotherapy or as part of a combination therapy

Endpunkte:

- PFS, OS, and safety (grade 3/4 adverse events [AEs], serious adverse events [SAEs], and discontinuations due to AEs)

Recherche/Suchzeitraum:

- between January 2013 and June 2015

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 (15 presented in full publications, and one presented in a conference abstract.
- Two additional publications were identified for inclusion through manual searches of conference abstracts, for a total of 18 publications reporting on 17 trials.
- A further two publications were identified providing safety data not available in the principal publications.

Charakteristika der Population:

Table 2. Summary of baseline patient characteristics from the primary analysis network.

Study	Treatment	N	Age, median (range)	ISS Stage III, *n* (%)
MM-020 (FIRST) [5,21]	Rd	535	73 (44–91)	216 (40.4)
	MPT	547	73 (51–92)	224 (41)
IFM 99/06 [16]	MP	196	(65–75)	54 (27.6)
	MPT	125	(65–75)	32 (25.6)
IFM 01/01 [17,37]	MP	116	(75–89)	NR
	MPT	113	(75–89)	NR
VISTA [30]	MP	338	71 (48–91)	115 (34)
	VMP	344	71 (57–90)	119 (34.9)
Sacchi et al. [18]	MP	54	79 (68–88)	16 (29.6)
	MPT	64	76 (66–89)	14 (21.9)

ISS: international staging system; NR: not reported; MP: melphalan and prednisone; MPT: melphalan, prednisone, and thalidomide; VMP: bortezomib, melphalan and prednisone.

Qualität der Studien:

- Overall, included trials presented minimal risk of bias.

Studienergebnisse:

- Primary analysis network: The primary analysis network was composed of five trials evaluating Rd, VMP, MP and MPT. Comparisons were evaluated using Rd as the reference treatment.
  - Analyses of OS using fixed effects NMA models documented a significantly lower risk of death with Rd treatment until progression compared to all tested treatment regimens (HRs [95% credible interval (CrI)]: VMP, 0.66 [0.46–0.93]; MPT, 0.75 [0.62–0.90]; MP, 0.46 [0.34–0.60]).
  - Similarly, a fixed effects analysis of PFS results showed a significantly lower risk of progression or death with Rd treatment until progression compared to all tested treatment regimens (HR [95% CrI]: VMP, 0.70 [0.49–0.99], MPT, 0.69 [0.59–0.80]; MP, 0.39 [0.31–0.50])

- Of note, the HRs and CrIs for MPT and VMP substantially overlapped for both OS and PFS evaluations, suggesting little difference between these regimens, although direct comparisons were not made.

- Sensitivity analyses:
  - A sensitivity analysis was conducted on a broader network of 11 trials to evaluate the effect of combining all trials that evaluated MPT and MPT-T treatments as well as any study comparator with a one- to two-degree linkage to either of these treatments in the network. This analysis added six trials to the primary analysis, including five arms assessing MPT-T, one assessing MPR, and two assessing MPR-R.
  - The sensitivity analysis for OS indicated a higher level of heterogeneity, as the CrIs were somewhat wider compared with the primary network analysis, although all HR values significantly favored Rd. This analysis showed a significantly lower risk of death with Rd dosed until progression compared with all other investigated interventions, including MP, MPT, MPR, MPR-R, MPT-T, and VMP (HR [95% CrI]): MP 0.46 [0.34–0.60]; MPT 0.75 [0.62–0.90]; MPR 0.38 [0.23–0.60]; MPR-R 0.47 [0.31–0.71]; MPT-T: 0.46 [0.33–0.64]; VMP 0.66 [0.46–0.93].
  - In terms of PFS, the sensitivity analysis also showed that all HR values significantly favored Rd, including MP, MPT, MPR, MPR-R, MPT-T, and VMP (HR [95% CrI]): MP 0.39 [0.31–0.50]; MPT 0.69 [0.59–0.80]; MPR 0.39 [0.26–0.58]; MPR-R 0.64 [0.46–0.89]; MPT-T: 0.60 [0.45–0.79]; VMP 0.70 [0.49–0.99].

- An additional sensitivity analysis was conducted evaluating all 17 trials identified from the systematic literature search. This analysis demonstrated a statistically significant lower risk of death with Rd treatment until progression compared to all thalidomide- or bortezomib-based regimens, regardless of treatment duration (data not shown).

Table 1. Extracted data from RCTs in the primary analysis and sensitivity analysis networks.

Study Group [Reference]	Comparison (N patients)	OS HR (95% CI)	PFS HR (95% CI)
Primary analysis			
MM-020 (FIRST) [5,21]	Rd (535) versus MPT (547)	0.75 (0.62–0.90)	0.69 (0.59–0.80)
IFM 99/06 [16]	MPT (125) versus MP (196)	0.59 (0.46–0.81)	0.51 (0.39–0.66)
IFM 01/01 [17,37]	MPT (113) versus MP (116)	0.68 (0.48–0.96)[a]	0.62 (0.47–0.82) [a]
VISTA [30]	VMP (344) versus MP (338)	0.70 (0.57–0.85)	0.56 (0.43–0.72)
Sacchi et al., 2011 [18]	MPT (64) versus MP (54)	0.42 (0.18–0.98)[a]	0.67 (0.38–1.18)[b]
Additional studies in sensitivity analysis			
TMSG [22,37]	MPT-T (58) versus MP (57)	0.86 (0.46–1.60)[d]	0.70 (0.42–1.17)[d]
GIMEMA [26,37]	MPT-T (167) versus MP (164)	1.04 (0.76–1.44)	0.63 (0.48–0.81)
MM-015 [28]	MPR (153) versus MPR-R (152)	1.27 (0.85–1.89)[a]	2.04 (1.43–2.94)[a]
	MP (154) versus MPR-R (152)	1.05 (0.69–1.60)[a]	2.50 (1.75–3.57)[a]
EIA06 [34]	MPT-T (154) versus MPR-R (152)	1.00 (0.67–1.50)[c]	0.84 (0.64–1.09)
NMSG [32,37]	MPT-T (182) versus MP (175)	1.12 (0.85–1.47)[d]	0.89 (0.70–1.13)[d]
HOVON 49 [33,37]	MPT-T (165) versus MP (168)	0.84 (0.61–1.16)[b]	0.54 (0.38–0.76)[b]
Additional studies in full sensitivity analysis			
IFM 95/01 [23]	MD (118) versus MP (122) D (127) versus MP (122) D-IFN (121) versus MP (122)	0.85 (0.62–1.17)[b] 1.14 (0.84–1.55)[b] 1.10 (0.80–1.50)[b]	0.86 (0.65–1.13)[b] 1.70 (1.30–2.22)[b] 1.46 (1.12–1.92)[b]
GEM05 [24]	VMP (130) versus VTP (130)	1.20 (0.60–2.40)	1.20 (0.90–1.70)
MRC Myeloma IX [25]	MP (423) versus CTD (426)	0.89 (0.74–1.08)	0.82 (0.70–0.96)
Palumbo et al. [27]	VMPT + VT (254) versus VMP (257)	0.70 (0.52–0.92)	0.58 (0.47–0.71)
Palumbo et al. [29]	MPR/CPR (430) versus Rd (211)	0.93 (0.60–1.41)	0.86 (0.66–1.12)
San Miguel et al. [31]	VMP + S (52) versus VMP (54)	1.00 (0.33–3.00)[c]	1.00 (0.58–1.75)[b]

CTD: cyclophosphamide, thalidomide, and dexamethasone; D: dexamethasone; D-IFN: dexamethasone and interferon; MP: melphalan and prednisone; MPR/CPR; melphalan, prednisone, and lenalidomide or cydophosphamide, prednisone, and lenalidomide; MPT: melphalan, prednisone, and thalidomide; MPT + T; melphalan, prednisone, and continuous thalidomide; MPR; melphalan, prednisone, and lenalidomide; MPR + R; melphalan, prednisone, and continuous lenalidomide; Rd; lenalidomide and dexamethasone; VMP: bortezomib, melphalan, and prednisone; VMP + S; bortezomib, melphalan, prednisone, and siltuximab; VMPT + VT: melphalan, prednisone, and continuous bortezomib and thalidomide; VTP: bortezomib, thalidomide, prednisone.
[a]Confidence interval estimated from *p* value.
[b]Hazard ratio and confidence interval estimated from the Kaplan–Meier curve.
[c]Hazard ratio and confidence interval estimated from number of deaths and survival rate.
[d]Data obtained from meta-analysis [37].

Anmerkung/Fazit der Autoren

In this analysis, Rd was associated with a significant PFS and survival advantage versus other first-line treatments (VMP, MPT, MP), challenging the role of alkylators in this setting.

Blommestein et al., 2019 [3].

Efficacy of first-line treatments for multiple myeloma patients not eligible for stem cell transplantation: a network meta-analysis.

Fragestellung

a network meta-analysis for NTE MM patients that synthesizes direct and indirect evidence and enables a comparison of all treatments.

Methodik

Population:

- newly diagnosed adult patients with MM

Intervention/Komparator:

- all treatment options for NTE NDMM (siehe Ergebnisteil)

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- EMBASE®, MEDLINE®, MEDLINE®-in-Process and the Cochrane Central Register of Controlled Trials for January 1999 to March 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 RCTs: These 24 RCTs included 21 treatment options: 1) Dexamethasone (D), 2) Dexamethasone-Interferon alpha (DI), 3) Melphalan 100 (M100), 4) Melphalan-Dexamethasone (MD), 5) Melphalan-Prednisone (MP), 6) Thalidomide-Dexamethasone (TD), 7) Cyclophosphamide-Thalidomide-Dexamethasone (CTD), 8) Cyclophosphamide-Thalidomide-Dexamethasone (attenuated) [CTD(a)], 9) Melphalan-Prednisone-Thalidomide/Melphalan-Prednisone-Thalidomide and Thalidomide maintenance (MPT/MPT-T), 10) Bortezomib-Dexamethasone (VD), 11) Bortezomib-Thalidomide-Dexamethasone (VTD), 12) Bortezomib-Melphalan-Prednisone (VMP), 13) Bortezomib-Thalidomide-Prednisone (VTP), 14) Bortezomib-Melphalan- Prednisone-Thalidomide and Bortezomib-Thalidomide (VMPTVT), 15) Cyclophosphamide-Prednisone-Lenalidomide (CPR), 16) Lenalidomide-Dexamethasone (Rd), 17) 18 cycles Lenalidomide-Dexamethasone (Rd18), 18) Melphalan-Prednisone-Lenalidomide (MPR), 19) Melphalan-Prednisone-Lenalidomide and Lenalidomide maintenance (MPR-R), 20) Bortezomib-Lenalidomide-Dexamethasone (VRd), 21) Daratumumab-Bortezomib-Melphalan-Prednisone (DaraVMP).

Charakteristika der Population:

- Most trials (21 out of 24) investigated iMID-based regimens (thalidomide or lenalidomide). Since MP has been the standard treatment for decades, MP was the comparator in 12 trials.
- PFS was the primary end point for 13 trials. The median age of the patient population was reported by most trials and ranged from 64 to 79 years. While some trials included patients aged <65 years, either because of choosing broader age limits or because of including patients who were not eligible for SCT independent of age, most trials only included patients aged ≥65 years.

Qualität der Studien:

Author	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors: efficacy (detection bias)	Blinding of outcome assessors: safety (detection bias)	Incomplete outcome data: efficacy (attrition bias)	Incomplete outcome data: safety (attrition bias)	Selective reporting (reporting bias)	Other bias
Facon	2006	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Facon	2007	Low risk	Unclear	High risk	Low risk	Low risk	High risk	High risk	Unclear	High risk
Morgan	2013	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Rajkumar	2008	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Ludwig	2009	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Palumbo	2008	Low risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	Unclear	High risk
Hulin	2009	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Waage	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Beksac	2010	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Wijermans	2010	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Sacchi	2011	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Hungria	2016	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	High risk
San Miguel	2008	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Mateos	2014	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Niesvizky	2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Palumbo	2014	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Zonder	2011	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Unclear	Unclear	High risk
Benboubkher	2014	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Zweegman	2016	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Stewart	2015	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Magarotto	2016	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk
Palumbo	2012	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Durie	2017	Low risk	Low risk	High risk	Low risk	Low risk	Unclear	Unclear	Unclear	High risk
Mateos	2018	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk

Studienergebnisse:

- All first-line NTE NDMM treatment options were better compared to the reference treatment dexamethasone (i.e. reducing the risk of progression or death compared to dexamethasone). HRs ranged between 0.19-0.90; however, not all treatments were statistically significantly different from dexamethasone, because of wide 95%CIs.
- DaraVMP and VMPT-VT were identified as the most effective treatment options as they had the highest and almost similar P-scores (i.e. a 96% and 93% certainty that this treatment is better than another treatment, averaged over all competing treatments) and most favorable relative treatment effects compared to dexamethasone (i.e. HR: 0.19, 95%CI: 0.08-0.45 and HR 0.22, 95%CI: 0.10-0.51 for DaraVMP and VMPT-VT, respectively).
- The HRs and 95%CIs for currently recommended treatments, VRd, VMP and Rd compared to dexamethasone, were 0.31 (95%CI: 0.16-0.59), 0.39 (95%CI: 0.20-0.75), and 0.44 (95%CI: 0.29-0.65), respectively. Selecting MPT as a reference treatment does not change the hierarchy of the treatments as the P-score values do not change if one considers a different reference treatment. Compared to MPT, only DaraVMP had a statistically lower HR for PFS (HR 0.41, 95%CI: 0.19-0.91; P<0.05).

Scenario analysis network meta-analysis

- In order to rule out that grouping of MPT and MPT-T would affect the outcome of the analysis, we performed a scenario in which we grouped IFM 01/01, IFM 99/06 and Sacchi et al. 2011, as MPT and GIMEMA, HOVON49, TMSG and NMSG as MPT-T. The MPT-T group was connected in the network to the MPT-T arm from the HOVON87 trial and the ECOG E1A06 trial.
- Overall, the results were comparable to the base case: We found similar results for MPT (HR 0.46, 95%CI: 0.30-0.71) and MPT-T (HR 0.47, 95% CI 0.30-0.73) compared to D.
- The second scenario, based on the trials included by Weisel et al.,(siehe oeben [12]) showed lower HRs for PFS for Rd compared to VMP, MPT and MP, but the 95%CI for VMP overlapped with Rd [Rd vs. VMP: HR 0.73, 95%CI: 0.48-1.11. (…)

Anmerkung/Fazit der Autoren

In addition to identifying the most effective treatment options, we illustrate the additional value and evidence of network meta-analysis in clinical practice. In the current treatment landscape, the results of network meta-analysis may support evidence-based decisions and ultimately help to optimize treatment and outcomes of NTE MM patients.

Chen M et al., 2018 [4]

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-ineligible patients in induction treatment, 11 studies involving 3725 patients reported 385 serious infection events.
  - Patients using IMiDs for therapy demonstrated a significantly increased risk for serious infection compared to non-IMiD therapy (RR = 1.59, 95% CI 1.31–1.93, p < 0.01). We rated the quality of evidence as moderate because of risk of bias.
  - The subgroup analysis by the type of intervention showed that patients who received melphalan-prednisolone-thalidomide for therapy demonstrated a significantly increased risk for serious infection compared to melphalan-prednisolone therapy (RR = 1.66, 95% CI 1.26–2.18, p < 0.01).
  - Nine trials reported a total of 210 infection events in 1517 patients with MM who used thalidomide-based regimen treatment for induction. When pooled the data, patients using thalidomide-based regimens for induction treatment demonstrated a significantly increased risk for serious infection versus control (pooled RR = 1.60, 95% CI 1.30–1.97, p < 0.01). However, the risk for serious infection in patients who received lenalidomide-based regimens for induction treatment was consistent with the control (RR = 1.54, 95% CI 0.95–2.48, p = 0.081). We graded the results as low due to 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 ungeeignete Patienten.

3.4 Leitlinien

NICE, 2016 [10].

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).]

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

Patients > 65 Years Old or Transplant Ineligible:

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, combinations of melphalan and prednisone with novel agents (thalidomide, lenalidomide, or bortezomib) have been shown to be superior to melphalan and prednisone alone as initial therapy for transplant ineligible patients. The standard therapy for these patients should therefore include a novel agent, alkylator, and steroids. However, in frail patients, and those with significant com-morbidities or advanced age (>75 years), there is an increased risk of toxicities. For these patients, consideration should be given to dose reductions of the initial regimen, and/or the use of two-drug combinations such as RD or VD79.

Referenzen aus Leitlinie:
79. Palumbo A and Anderson K. Multiple Myeloma nejm 2011;364:1046

Bortezomib-Based Regimens:

The VISTA trial randomized patients to bortezomib + melphalan + prednisone (VMP) versus MP for 9 cycles80. Regimens:

- MP (melphalan + prednisone) cycles 1-9 (6 week cycles)
  - melphalan 9mg/m2 days 1-4
  - prednisone 60mg/m2 days 1-4
- VMP (bortezomib + melphalan + prednisone)
  - cycles 1-4 (6 week cycles): MP plus bortezomib 1.3mg/m2 IV days 1,4,8,11,22,25,29,32
  - cycles 5-9 (6 week cycles): MP plus bortezomib 1.3mg/m2 IV days 1,8,22,29

The mean response duration was 19.9 months in the bortezomib group versus 13.1 months in the control group. Median TTP was 24.0 months in the bortezomib group versus 16.6 months in the control group (HR= 0.48). OS after a median follow-up of 16.3 months was not reached in either group: 45 patients (13%) in the bortezomib group and 76 patients (22%) in the control group died. The hazard ratio for overall survival was 0.61 for the bortezomib group (p=0.008)

A modified VISTA regimen has also been used, with 6 cycles of VMP followed by VP maintenance81:

- Cycle 1 (6 week cycle):
  - bortezomib 1·3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32
  - melphalan 9 mg/m² on days 1-4
  - prednisone 60 mg/m² on days 1-4
- Cycle 2-5 (5 week cycles):
  - bortezomib 1·3 mg/m² on days 1, 8, 15, and 22)
  - melphalan 9 mg/m² on days 1-4
  - prednisone 60 mg/m² on days 1-4
- Maintenance (up to 3 years):
  - bortezomib 1·3 mg/m² on days 1, 4, 8, and 11 every 3 months
  - plus either prednisone (50 mg every other day) or thalidomide (50 mg per day)

Referenzen aus Leitlinie:
81. Mateos MV et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly Multiple Myeloma patients included in the GEM2005MAS65 trial Blood. 2012 Aug 13

The VMP regimen was compared to VMP plus thalidomide followed by maintenance with bortezomib plus thalidomide (VMPT-VT)82. VMPT followed by VT as maintenance was superior to VMP alone in patients with multiple myeloma who are ineligible for autologous stem-cell transplantation. The 3-year PFS was 56% in patients receiving VMPT-VT and 41% in those receiving VMP (P = .008). Complete response were 38% in the VMPT-VT group and 24% in the VMP group (P < .001). The 3-year overall survival was 89% with VMPT-VT and 87% with VMP (HR, 0.92; 95% CI, 0.53 to 1.60; P = .77). Grade 3 to 4 neutropenia (38% v 28%; P = .02), cardiologic events (10% v 5%; P = .04), and thromboembolic events (5% v 2%; P = .08) were more frequent among patients assigned to the VMPT-VT group than among those assigned to the VMP group; treatment-related deaths were 4% with VMPT-VT and 3% with VMP.

Referenzen aus Leitlinie:

82. Palumbo et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial.J Clin Oncol. 2010 Dec 1;28(34):5101-9.

VMP-VT regimen:

Cycles 1-4 (42 day cycles):

- Melphalan 9 mg/m2 on days 1 to 4
- Prednisone 60 mg/m2 on days 1 to 4
- Bortezomib 1.3 mg/m2 iv on days 1, 4, 8, 11, 22, 25, 29, and 32
- Thalidomide 50 mg per day continuously.

Cycles 5-9

- Melphalan 9 mg/m2 on days 1 to 4
- Prednisone 60 mg/m2 on days 1 to 4
- Bortezomib 1.3 mg/m2 iv on days 1, 8, 22, and 29
- Thalidomide 50 mg per day continuously.

Maintenance:

- After the last VMPT course, patients received maintenance therapy with bortezomib 1.3 mg/m2 every 14 days and thalidomide 50 mg per day for 2 years or until progression or relapse

The combination of cyclophosphamide, bortezomib and dexamethasone has been shown in a number of phase II trials to be well tolerated, and produces superior response rates83. It is currently the regimen of choice for first line therapy for non-transplant eligible myeloma patients.

- 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

Patients should receive 9-12 cycles followed by maintenance bortezomib (1.3mg/m2 every 2 weeks for 2 years).

Referenzen aus Leitlinie:

83. Khan ML, Reeder CB, Kumar SK, et al. A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma.Br J Haematol. 2012 Feb;156(3):326-33. doi: 10.1111/j.1365-2141.2011.08949.x. Epub 2011 Nov 23.

<u>Lenalidomide-Based Regimens:</u>

Lenalidomide is currently not funded for first-line use in multiple myeloma.

In the MM015 trial, 459 patients were randomly assigned to receive melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) therapy until a relapse or disease progression or to receive MPR or MP without maintenance therapy84. The median progression-free survival was significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio, 0.49; P<0.001) or MP (13 months; hazard ratio, 0.40; P<0.001). Response rates were superior with MPR-R and MPR (77% and 68%, respectively, vs. 50% with MP; P<0.001 and P=0.002, respectively, for the comparison with MP). The progression-free survival benefit associated with MPR-R was noted in patients 65 to 75 years of age but not in those older than

75 years of age (P=0.001 for treatment-by-age interaction). The 3-year rate of second primary tumors was 7% with MPR-R, 7% with MPR, and 3% with MP.

MPR-R regimen: Nine 28-day cycles of

- Melphalan 0.18 mg/kg days 1 through 4
- Prednisone 2 mg per kilogram days 1 through 4
- Lenalidomide 10 mg on days 1 through 21
- Followed by lenalidomide maintenance (10 mg on days 1 through 21 of each 28-day cycle) until disease progression or the development of unacceptable adverse effects

Referenzen aus Leitlinie:
84. Palumbo A et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma.N Engl J Med. 2012 May 10;366(19):1759-69.

The FIRST study compared MPT for 12 cycles (18months) to lenalidomide and dexamethasone for 18 cycles (18months) and len/dex until disease progression in newly diagnosed myeloma patients not eligible for stem cell transplant85. The continuous Rd strategy was superior to MPT with improved response rate, PFS and duration of response. Overall survival at 4 years was improved with continuous Rd, but this did not reach statistical significance (4-year OS 59% vs 51%, p=0.0168).

Referenzen aus Leitlinie:
85. Facon T, et al. Initial Phase 3 Results Of The First (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) Trial (MM-020/IFM 07 01) In Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible For Stem Cell Transplantation (SCT). Blood: November 15, 2013; 122 (21)

Thalidomide-Based Regimens:

- The IFM99-06 and IFM 01-01 trials also reported higher OS rates.86, 87
- MPT was also shown in one trial (IFM99-06) to be superior to tandem transplant with reduced intensity melphalan conditioning (100 mg/m2 x 2).86
- Increased toxicity (DVT/pulmonary embolism 12% versus 4% with MP) and higher rates of neutropenia have been reported with MPT therapy.

Table 5. Melphalan + Prednisone + Thalidomide (MPT) Regimens

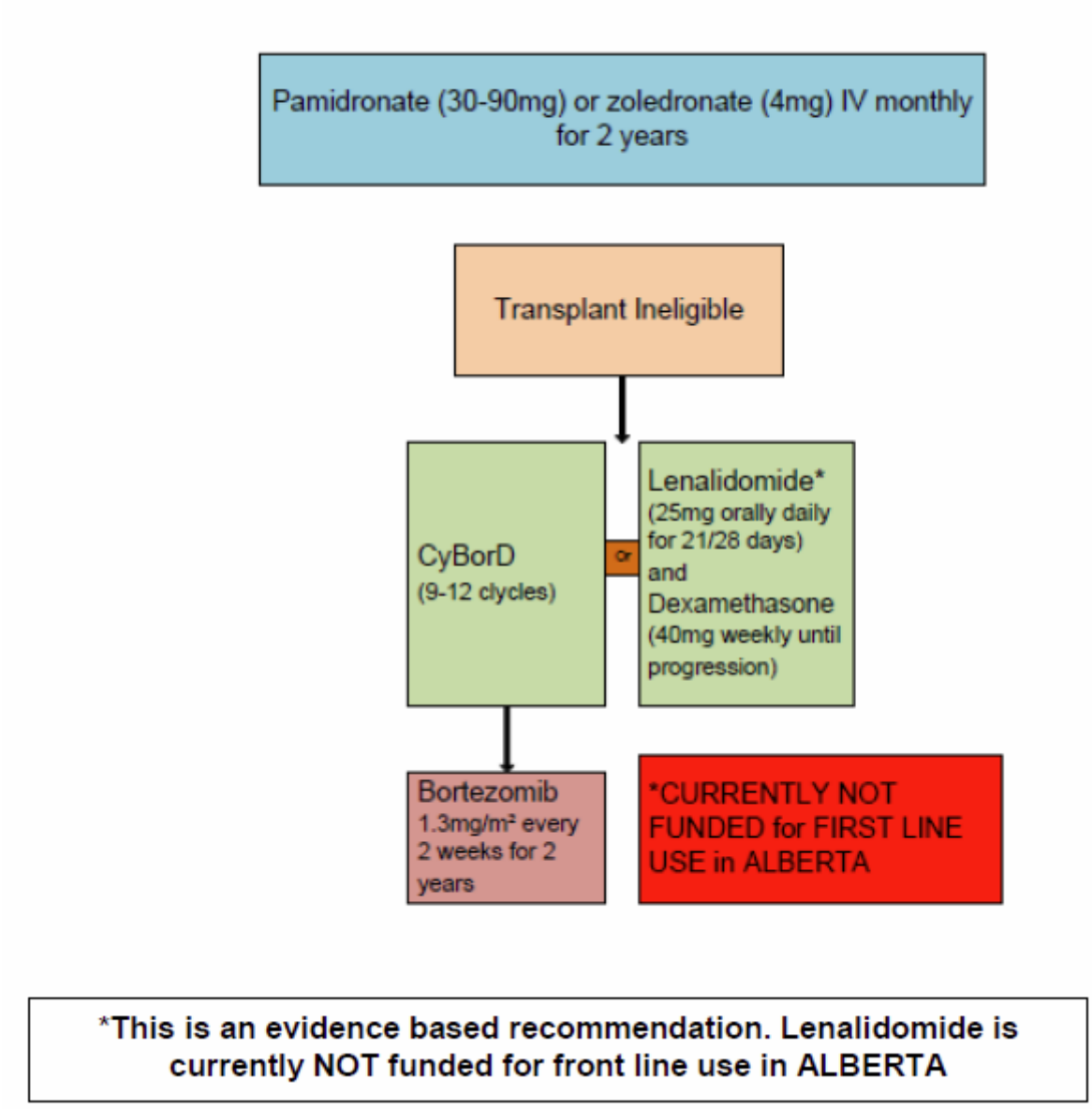
Regimen	Dosing
IFM99-06 Regimen[86]	Melphalan 0.25 mg/kg on days 1–4 q 6 weeks x 12 cycles Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles Thalidomide at the maximum tolerated dose, but < 400 mg/day, x 12 cycles.
IFM01-01 Regimen[87] (patients >75 years)	Melphalan 0.20 mg/kg on days 1–4 q 6 weeks x 12 cycles Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles Thalidomide 100 mg PO daily, x 12 cycles.
Palumbo Regimen[88]	Melphalan 4 mg/m^2 on days 1–7 q 4 weeks x 6 cycles Prednisone 40 mg/m^2 on days 1–7 q 4 weeks x 6 cycles Thalidomide 100 mg /day continuously until relapse or progressive disease

- Thrombosis prophylaxis is required with the use of thalidomide or lenalidomide. There is no consensus at the present time regarding the optimal DVT/pulmonary embolism prophylaxis. Acceptable options include: o Daily ASA (81 or 325 mg)
  - o Prophylactic dose of low molecular weight heparin (LMWH)
  - o Coumadin with therapeutic INR (2-3)

Summary:

- CYBOR-D, VMP, and lenalidomide* plus dexamethasone (given until disease progression) are suitable options for newly diagnosed, transplant ineligible myeloma patients. However, lenalidomide is currently not approved for initial therapy

- Therefore, CYBORD for 9-12 cycles is the recommended therapy for newly diagnosed, transplant ineligible patients. Alternatively, patients may be treated with VMP for 9 cycles. Following initial therapy, all patients should receive maintenance with bortezomib 1·3 mg/m² every 2 weeks for 2 years
- Bortezomib based therapy is preferred over lenalidomide based therapy for patients with 17p deleted myeloma.



Moreau P et al., 2017 [9].

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

Elderly patients (non-transplant setting):

- The two following options are recommended based on data from randomised phase III trials [I, A]: bortezomib (administered subcutaneously)/melphalan/prednisone (VMP) or lenalidomide plus low-dose dexamethasone (Rd); both VMP and Rd are approved in this setting by the European Medicines Agency (EMA). Rd is approved until progression of the disease. Melphalan/prednisone/thalidomide (MPT) is also approved by the EMA, but is inferior to Rd in terms of PFS and OS. Bortezomib cyclophosphamide and dexamethasone (VCD) is not EMA approved (no controlled data), but is widely used and induces high response rates and prolonged PFS [III, A]. Rd has recently been compared prospectively with Rd plus bortezomib (VRd), and the addition of bortezomib resulted in significantly improved PFS and OS and had an acceptable risk–benefit profile. Nevertheless, this triplet combination is not yet approved by the EMA. Bendamustine plus prednisone is also approved by the EMA in patients who have clinical neuropathy at time of diagnosis, precluding the use of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen [II, C].
- Melphalan/prednisone/lenalidomide (MPR) has been evaluated in two prospective randomised studies versus melphalan and prednisone (MP) and versus MPT, but MPR was not superior to the other combinations with a fixed number of cycles [II, C]. This triplet combination is approved by the EMA but is not routinely used and cannot be considered as a standard of care.
- Cyclophosphamide/thalidomide/dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP [II, C].

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.

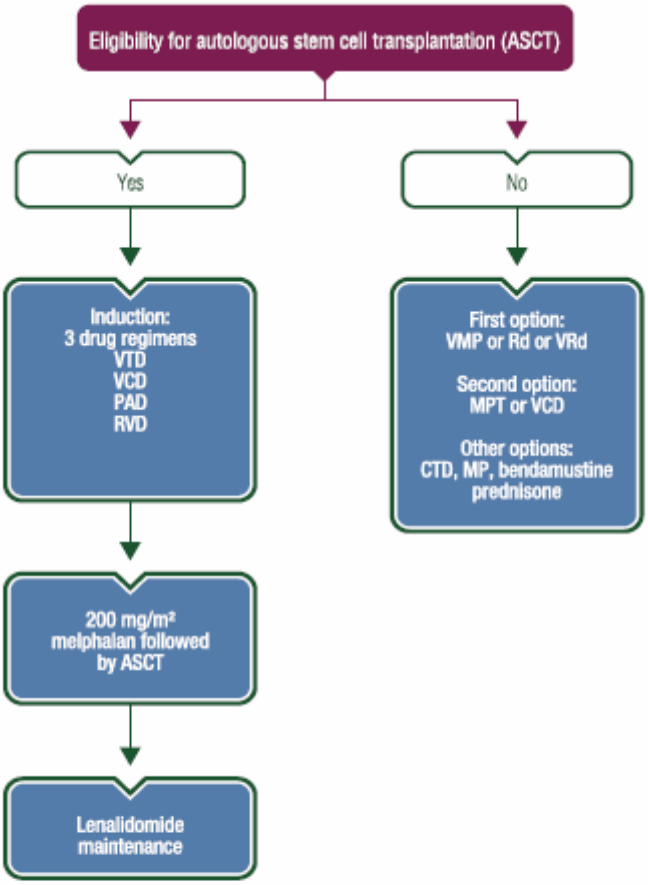


Figure 1. Front-line treatment of symptomatic multiple myeloma outside clinical trials.
CTD, cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; PAD, bortezomib, doxorubicin, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RVD, lenalidomide,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

Mikhael Jet al., 2019 [8].

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 considers the 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 the ExpertPanel's confidence in 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 indication of the Expert Panel'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 Ineligible

- Recommendation 5.1. Initial treatment recommendations for patients with multiple myeloma who are transplant ineligible should be individualized based on shared decision making between physicians and patients. Multiple factors should be considered; disease-specific factors such as stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, functional status, frailty status, and patient preferences should also be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 5.2. Initial treatment of patients with multiple myeloma who are transplant ineligible should include at minimum a novel agent (immunomodulatory drug or PI) and a steroid if possible (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 5.3. Triplet therapies for patients with multiple myeloma who are transplant ineligible, including bortezomib, lenalidomide, dexamethasone, should be considered. Daratumumab plus bortezomib plus melphalan plus prednisone may also be considered (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

- Recommendation 5.4. Physicians/patients should balance the potential improvement in response and disease control with a possible increase in toxicity. Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 5.5. Continuous therapy should be offered over fixed-duration therapy when initiating an immunomodulatory drug or PI-based regimen (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).
- Recommendation 6.1. The goal of initial therapy for transplant-ineligible patients should be achievement of the best quality and depth of remission (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 6.2. Depth of response for all patients should be assessed by IMWG criteria regardless of transplant eligibility (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 6.3. There is insufficient evidence to support change in type and length of therapy based on depth of response as measured by conventional IMWG approaches or MRD (Type: informal consensus; Evidence quality: low, harm outweighs benefit; Strength of recommendation: moderate).
- Recommendations 6.4. Upon initiation of therapy, one should define patient-specific goals of therapy. Quality of-life assessment (including symptom management and tolerability of treatment) should be assessed at each visit to determine if the goals of therapy are being maintained/met, and this should influence the intensity and duration of treatment. Redefining the goals prospectively, based on response, symptoms, and quality of life, is recommended (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).
- Recommendation 6.5. It is recommended that patients be monitored closely with consideration of dose modifications based on levels of toxicity, neutropenia, fever/infection, tolerability of adverse effects, performance status, liver and kidney function, and in keeping with the goals of treatment. (Type: informal consensus; Evidence quality: low, 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]))))))
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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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