Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-281 Decitabin/Cedazuridin

Stand: Januar 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Decitabin/Cedazuridin

[zur Behandlung von erw. Pat. mit einer neu diagnostizierten akuten myeloischen Leukämie (AML), für die eine intensive Chemotherapie nicht geeignet ist]

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 nach §35a SGB V: - Venetoclax (Beschluss vom 02. Dezember 2021) - Glasdegib (Beschluss vom 18. Februar 2021) - Decitabin (Beschluss vom 02. Mai 2013) Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie (Stand: 08. November 2022) Arzneimittel, die in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind - Hydroxycarbamid bei chronischer myelomonozytärer Leukämie (CMML) oder bei CMML nach Übergang in eine akute myeloische Leukämie.
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 bewertendes Arzneimittel:	
Decitabin/Cedazuridin N.N. Inaqovi	Geplantes Anwendungsgebiet laut Beratungsanforderung: Inaqovi ist angezeigt zur Behandlung von erwachsenen Patienten mit einer neu diagnostizierten akuten myeloischen Leukämie (AML), für die eine intensive Chemotherapie nicht geeignet ist
Azacitidin L01BC07 Vidaza	Vidaza ist angezeigt zur Behandlung von erwachsenen Patienten, die für eine Transplantation hämatopoetischer Stammzellen (HSZT) nicht geeignet sind und eines der folgenden Krankheitsbilder aufweisen: […] - akute myeloische Leukämie (AML) mit 20-30 % Blasten und Mehrlinien-Dysplasie gemäß Klassifikation der World Health Organisation (WHO) - AML mit > 30 % Knochenmarkblasten gemäß WHO-Klassifikation.
Cytarabin L01BC01 Cytarabin Accord	Zur Induktion der Remission bei akuter myeloischer Leukämie bei Erwachsenen und zur Behandlung anderer akuter Leukämien bei Erwachsenen und Kindern.
Daunorubicin L01DB02 Daunoblastin	<u>Erwachsene</u> Remissionsinduktion bei akuten lymphoblastischen bzw. lymphatischen (ALL) und bei akuten myeloischen Leukämien (AML). Die Anwendung erfolgt in Kombination mit anderen Zytostatika.
Decitabin L01BC08 Dacogen	Dacogen ist indiziert zur Behandlung erwachsener Patienten mit neu diagnostizierter de novo oder sekundärer akuter myeloischer Leukämie (AML) gemäß der Klassifikation der Weltgesundheitsorganisation (WHO), für die eine Standard-Induktionstherapie nicht in Frage kommt.
Doxorubicin L01DB01 Ribodoxo	[…] Remissionsinduktion bei akuter myeloischer Leukämie […]
Etoposid L01CB01 Etopophos	<u>Entscheidung der Europäischen Komission zur Harmonisierung der Fachinformation von Etopophos:</u> Etopophos ist angezeigt in Kombination mit anderen antineoplastisch wirksamen Präparaten zur Behandlung der akuten myeloischen Leukämie bei Erwachsenen und Kindern. (Stand Juni 2017; EMEA/H/A-30/1417; Entscheidung (2017)4521 of 26/06/2017)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Glasdegib L01XJ03 Daurismo	Daurismo wird angewendet in Kombination mit niedrig dosiertem Cytarabin (LDAC, low-dose cytarabine) für die Behandlung von neu diagnostizierter de novo oder sekundärer akuter myeloischer Leukämie (AML) bei erwachsenen Patienten, die nicht für eine Standard-Induktionschemotherapie infrage kommen.
Histamindihydro-chlorid L03AX14 Ceplene	Die Ceplene-Erhaltungstherapie ist indiziert für erwachsene Patienten mit akuter myeloischer Leukämie (AML) in erster Remission, die gleichzeitig mit Interleukin-2 (IL-2) behandelt werden. Die Wirksamkeit von Ceplene wurde bei Patienten über 60 Jahren nicht völlig nachgewiesen.
Idarubicin L01DB06 Zavedos	Erwachsene: Zavedos ist in Kombination mit anderen Zytostatika (z. B. Cytarabin) zur Remissionsinduktion und Konsolidierung bei unvorbehandelten Patienten mit akuten myeloischen Leukämien (AML, ANLL) im Erwachsenenalter angezeigt.
Mitoxantron L01DB07 Ralenova	Mitoxantron ist indiziert zur Behandlung der akuten myeloischen Leukämie (AML) bei Erwachsenen.
Tioguanin L01BB03 Tioguanin-Aspen	Induktions- und Konsolidierungsphase der Behandlung der akuten myeloischen Leukämie (AML).
Venetoclax Venclyxto L01XX52	Venclyxto in Kombination mit einer hypomethylierenden Substanz wird angewendet zur Behandlung erwachsener Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML), die nicht für eine intensive Chemotherapie geeignet sind.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2022-B-281 (Decitabin/Cedazuridin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	2. Dezember 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AML	Akute myeloische Leukämie
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azacitidin
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
ECOG	Eastern Cooperative Oncology Group
ECRI	ECRI Guidelines Trust
FLT3	FMS-like tyrosine kinase 3
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HiDAC	High-dose cytarabine
HMA	Hypomethylating agents (Azacitidin und Decitabin)
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LDAC	low-dose Cytarabin
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Inaqovi ist angezeigt zur Behandlung von erwachsenen Patienten mit einer neu diagnostizierten akuten myeloischen Leukämie (AML), für die eine intensive Chemotherapie nicht geeignet ist.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *akuter myeloischer Leukämie (AML)* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.startpage.com) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 15.10.2021 durchgeführt, die folgende am 31.10.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 829 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 3 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Colunga-Lozano,et al., 2022 [1].

Less intensive antileukemic therapies (monotherapy and/or combination) for older adults with acute myeloid leukemia who are not candidates for intensive antileukemic therapy: a systematic review and meta-analysis

Fragestellung

comparative effectiveness and safety of low-intensity antileukemic therapies (monotherapy and/or combination) in older adults with newly diagnosed AML who are not candidates for intensive therapy

Methodik

Population:

- Pat. mit neu diagnostiziertem AML >55 J., die nicht für eine intensive Therapie in Frage kommen

Intervention:

- Gemtuzumab ozogamicin, low dose Cytarabin (LDCA), Azacitidine (AZA) und Decitabin (DEC) alleine oder in Kombination

Komparator:

- Siehe Intervention

Endpunkte:

- Mortalität, QoL, Funktionsstatus, Rezidiv, Remission, Toxizität Grad 3 oder höher

Recherche/Suchzeitraum:

- Recherche im August 2021 in Medline und Embase

Qualitätsbewertung der Studien:

- RCTs: Cochrane RoB
- Non-RCTs: ROBINS-I

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 RCTs (N=3.902)
- 10 non-RCTs (N=1.796) – hier nicht dargestellt

Charakteristika der Population:

- Alter im Median zwischen 67 und 76 J., follow-up im Median 7,4-40 Monate

Qualität der Studien:

- Geringes Biasrisiko in den Domänen sequence generation und concealment bei allen RCTs
- 3 RCTs mit hohem Risiko bei allocation concealment

Studienergebnisse:

- Gesamtmortalität:
  - AZA-Monotherapie vs. LDAC-Monotherapie, LDAC-Monotherapie vs. LDAC plus Volasertib, LDAC-Monotherapie vs. HMA: keine signifikanten Unterschiede zwischen den Behandlungsgruppen (7 RCTs (N=1.511)
  - AZA-Monotherapie vs. LDAC-Monotherapie: RR 0,78 (95%-CI 0,64;0,94), 1 RCT N=312)
- Komplette Remission (operationalisiert als event-free survival):
  - AZA-Monotherapie vs. AZA+Venetoclax: HR 1,59 (95%-CI 1,26;2.00), 1 RCT (N=488)
- Septischer Schock:
  - AZA-Monotherapie vs. LDAC-Monotherapie und AZA-Monotherapie vs. AZA plus Vorinostat: keine signifikanten Gruppenunterschiede (2 RCTs, N=421)
- Febrile Neuropenie:
  - AZA-Monotherapie vs. AZA plus Venetoclax: RR 0,45 (95%-CI 0,31;0,65), 1 RCT N=427)
  - Andere Vergleiche: keine signifikanten Unterschiede
- Pneumonie, Sepsis, Anämie, Neutropenie: keine signifikanten Unterschiede zwischen den Gruppen

Anmerkung/Fazit der Autoren

Our evidence suggests HMA therapies are acceptable options with similar efficacy and safety to other less-intensive treatment options. The certainty of the evidence was, however, low for most comparisons and outcomes, and there was no published evidence for several outcomes considered critical for decision-making.

Kommentare zum Review

Die RCT- und Non-RCT-Ergebnisse wurden getrennt berichtet, nur die Ergebnisse für RCTs wurden hier dargestellt.

Ergebnisse zu QoL oder Funktionsstatus nicht verfügbar.

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), Version 2.2022 [2].

Acute Myeloid Leukemia

Zielsetzung

The AML Panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) convenes annually to update recommendations for the diagnosis and treatment of AML in adults.

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund der Evidenzlage wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, unklar, ob eine Einbeziehung von Patientenvertretungen erfolgte;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche dargelegt, Systematik der Auswahl und Bewertung der Evidenz unklar;
- Verfahren zur Konsensfindung und externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig, die Verknüpfung mit der zugrundeliegenden Evidenz ist nur indirekt über den Hintergrundtext zu den Empfehlungen möglich;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

Prior to the update of this version of the NCCN Guidelines® for AML, an electronic search of the PubMed database was performed to obtain key literature in AML published since the previous Guidelines update […].

LoE/GoR

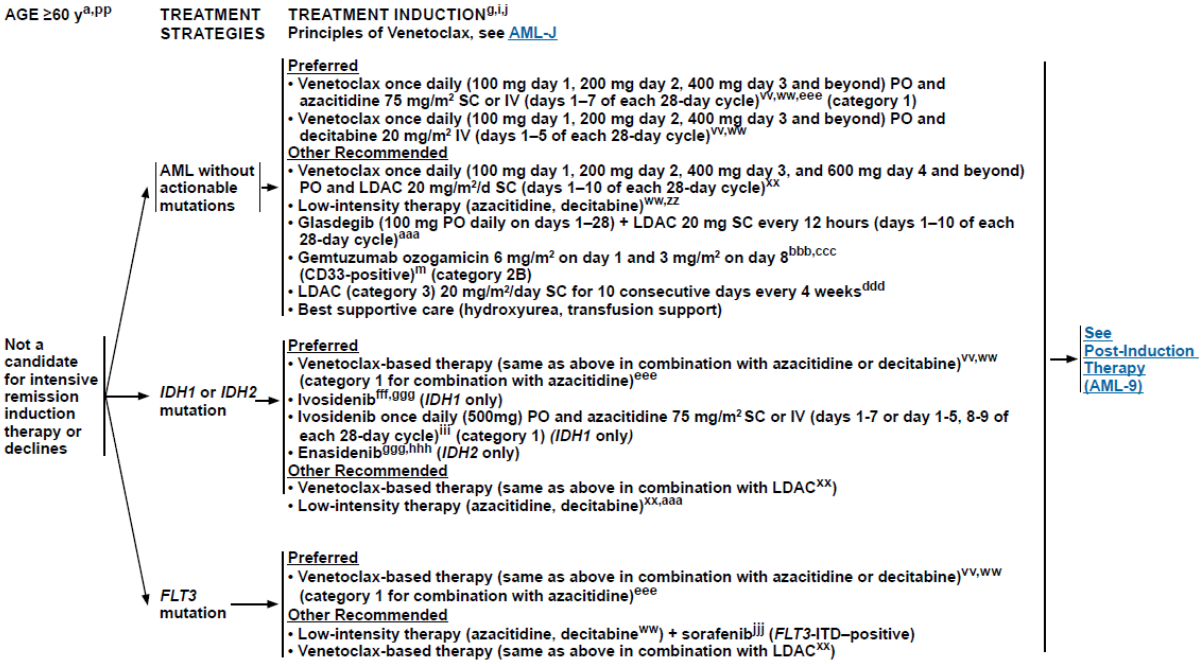
NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Empfehlungen für Patientinnen und Patienten >= 60 Jahre, die nicht für eine intensive Chemotherapie in Frage kommen:



FOOTNOTES FOR TREATMENT INDUCTION (AGE ≥60 YEARS)

[a] Patients with elevated blast counts are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include apheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.

[g] See Principles of Supportive Care for AML (AML-E).

[i] Consider referral to palliative care for consultation at the start of induction. LeBlanc TW, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc TW, et al. J Oncol Pract.2017;13:589-590. See NCCN Guidelines for Palliative Care.

[j] See General Considerations and Supportive Care for Patients Who Prefer Not to Receive Blood Transfusions (AML-D).

[m] Threshold for CD33 is not well-defined and may be ≥1%.

[pp] There is a web-based scoring tool available to evaluate the probability of complete response and early death after standard induction therapy in elderly patients with AML: http://www.aml-score.org/. Krug U, et al. Lancet 2010;376:2000-2008. A web-based tool to predict CR and early death can be found at: https://trmcalculator.fredhutch.org and Walter RB, et al. J Clin Oncol 2011;29:4417-4423. Factors in decisions about fitness for induction chemotherapy include age, performance status, functional status, and comorbid conditions. See NCCN Guidelines for Older Adult Oncology.

[vv] This regimen may be continued for patients who demonstrate clinical improvement (CR/CRi), with consideration of subsequent transplant, where appropriate. DiNardo CD, et al. Lancet Oncol 2018;19:216-228; Wei A, et al. Blood 2017;130:890; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[ww] Patients who have progressed to AML from MDS after significant exposure to HMAs (ie, azacitidine, decitabine) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naïve. Alternative treatment strategies should be considered. DiNardo CD, et al. Blood 2019;133:7-17.

[xx] Wei AH, et al. J Clin Oncol 2019;37:1277-1284.

[zz] In patients with AML with *TP53* mutation, a 10-day course of decitabine may be considered (Welch JS, et al. N Engl J Med 2016;375:2023-2036). Response may not be evident before 3–4 cycles of treatment with HMAs (ie, azacitidine, decitabine). Continue HMA treatment until progression if patient is tolerating therapy. Similar delays in response are likely with novel agents in a clinical trial, but endpoints will be defined by the protocol.

[aaa] This regimen is for treatment of newly diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (ie, severe cardiac disease, ECOG performance status ≥2, baseline creatinine >1.3 mg/dL) and has been associated with an improved OS in a randomized trial. Cortes JE, et al. Blood 2016;128:99.

[bbb] Amadori S, et al. J Clin Oncol 2016;34:972-979.

[ccc] Regimens that include gemtuzumab ozogamicin will not benefit patients with poor-risk disease.

[ddd] Kantarjian HM, et al. J Clin Oncol 2012;30:2670-2677.

[eee] DiNardo CD, et al. N Engl J Med 2020;383:617-629.

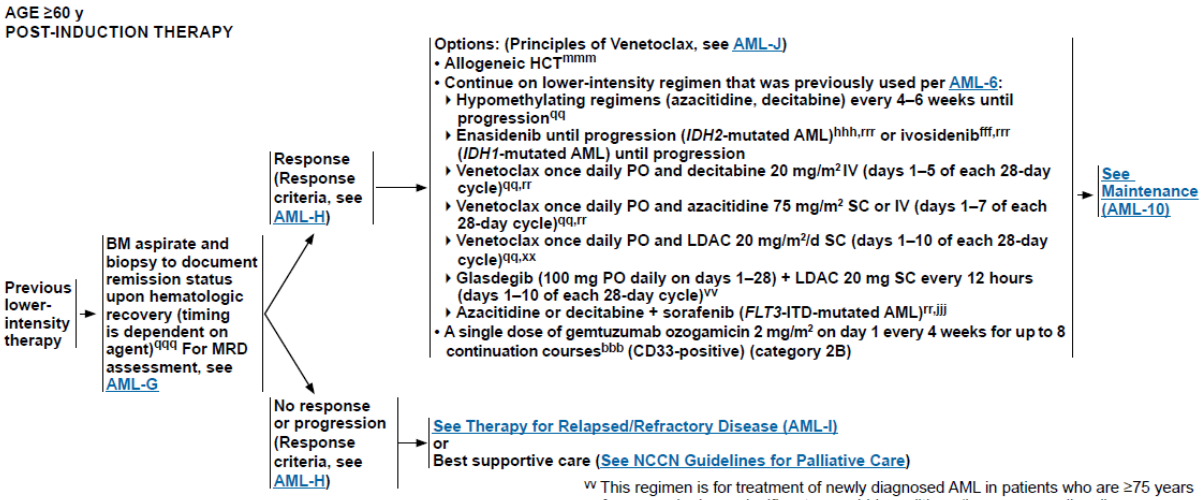
[fff] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Roboz GJ, et al. Blood 2020;135:463-471.

[ggg] When using this agent, monitor closely for differentiation syndrome and initiate therapy to resolve symptoms according to indications. Note that differentiation syndrome can occur later (up to several months after induction).

[hhh] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.

[iii] This regimen is approved for newly-diagnosed AML with an *IDH1* mutation who met at least one of the following criteria: age >75 years, baseline ECOG performance status of ≤ 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, creatinine clearance < 45 mL/min, or other comorbidity. Montesinos P, et al. N Engl J Med 2022;386:1519-153.

[jjj] Ohanian M, et al. Am J Hematol 2018;93:1136-1141.



[qq] This regimen may be continued for patients who demonstrate clinical improvement (CR/CRi), with consideration of subsequent transplant, where appropriate. DiNardo CD, et al. Lancet Oncol 2018;19:216-228; Wei A, et al. Blood 2017;130:890; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[rr] Patients who have progressed to AML from MDS after significant exposure to HMAs (ie, azacitidine, decitabine) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naïve. Alternative treatment strategies should be considered. DiNardo CD, et al. Blood 2019;133:7-17.

[xx] Wei AH, et al. J Clin Oncol 2019;37:1277-1284.

[vv] This regimen is for treatment of newly diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (ie, severe cardiac disease, ECOG performance status ≥2, baseline creatinine >1.3 mg/dL). Cortes JE, et al. Blood 2016;128:99-99.

[bbb] Amadori S, et al. J Clin Oncol 2016;34:972-979.

[fff] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Roboz GJ, et al. Blood 2020;135:463-471.

[hhh] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.

[jjj] Ohanian M, et al. Am J Hematol 2018;93:1136-1141.

[mmm] Patients who are deemed as candidates for HCT and who have an available donor should be transplanted in first remission.

[qqq] Response to treatment with enasidenib or ivosidenib may take 3–5 months.

[rrr] Enasidenib or ivosidenib increases the risk for differentiation syndrome and hyperleukocytosis that may require treatment with hydroxyurea and steroids.

- Hintergrundinformationen zu den Empfehlungen des NCCN für Erwachsene >= 60 Jahre finden sich im Anhang.
- Referenzen zu den Empfehlungen dieser LL finden sich im Anhang.

Sekeres MA et al, 2020 [3].

American Society of Hematology (ASH)

American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

Zielsetzung/Fragestellung

To provide evidence-based recommendations for management of older adults [*>=55 years*] with newly diagnosed AML, from the time of their diagnosis, through postremission therapy, and considerations for end-of-life/hospice care.

Table 2. Clinical questions formulated and prioritized

Questions determined by the panel
1. Should older adults with newly diagnosed AML who are candidates for antileukemic therapy receive antileukemic therapy instead of best supportive care only?
2. Should older adults with newly diagnosed AML considered candidates for antileukemic therapy receive intensive antileukemic therapy vs less-intensive antileukemic therapy?
3. Should older adults with newly diagnosed AML who achieve remission after at least 1 cycle of intensive antileukemic therapy receive postremission therapy vs no additional therapy?
4. Should older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy receive gemtuzumab ozogamicin, low-dose cytarabine, azacitidine, 5-d decitabine, or 10-d decitabine as monotherapy or in combination?
5. Should older adults with AML who received less-intensive antileukemic therapy and who achieved a response continue therapy indefinitely until progression/toxicity or be given therapy for a finite number of cycles?
6. Should older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life or hospice care) receive RBC transfusions, platelet transfusions, or both, vs no transfusions?

Methodik

<u>Grundlage der Leitlinie</u>

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

<u>Recherche/Suchzeitraum:</u>

- OVID Medline, EMBASE; up until 24 May 2019

<u>LoE/GoR</u>

- COCHRANE RoB; GRADE

Table 1. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not; decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences
Clinicians	Most individuals should follow the recommended course of action; formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences; decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences
Policy makers	The recommendation can be adopted as policy in most situations; adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator	Policy making will require substantial debate and involvement of various stakeholders; performance measures should assess whether decision-making is appropriate
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation; on occasion, a strong recommendation is based on low or very low certainty in the evidence; in such instances, further research may provide important information that alters the recommendations	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research; an evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps

Sonstige methodische Hinweise

- Methodisch hochwertige Leitlinie; beschränkt auf Erwachsene >=55 Jahre
- Diese LL enthält **keine Empfehlungen zur Risikostratifizierung nach FLT3-Mutationsstatus und keine Empfehlungen zum Einsatz von FLT3-Inhibitoren.** S. auch den Abschnitt *Limitations* aus der LL.

Empfehlungen

Recommendation 4a (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕◯◯)

For older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy, the ASH guideline panel suggests using either of the options when choosing between hypomethylating-agent monotherapy and low-dose-cytarabine monotherapy

Recommendation 4b (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯)

For older adults with AML considered appropriate for antileukemic therapy (such as hypomethylating agents [azacitidine and decitabine] or low-dose cytarabine) but not for intensive antileukemic therapy, the ASH guideline panel suggests using monotherapy with 1 of these drugs over a combination of 1 of these drugs with other agents.

Remarks: For patients treated with combination therapy, the agents for which there is evidence of effectiveness are low-dose cytarabine in combination with glasdegib, based on a small randomized trial, and hypomethylating agents or low-dose cytarabine in combination with venetoclax, based on promising data from phase 2 trials. These recommendations may change (favoring combination therapies over monotherapy) with upcoming reporting of results from randomized trials.

Hintergrund

Twenty studies[64,96,101,122,125,130,148-168] informed this recommendation question. For Recommendation 4a, 3 RCTs provided evidence for the comparison between azacytidine monotherapy and low-dose cytarabine monotherapy,[64,101,130] and 1 RCT[156] and 1 observational study[155] compared the effects of low-dose cytarabine monotherapy with the effects of decitabine monotherapy. In addition, there was 1 observational study comparing the effects of low-dose cytarabine monotherapy and either 1 of the hypomethylating agents. Within the category of hypomethylating agents, 3 observational studies

compared the effects of decitabine monotherapy and azacitidine monotherapy.[153,159,162] Wedid not find any randomized data comparing 5-day and 10-day decitabine monotherapy thatmet inclusion criteria (though 1 study of 71 patients[169] undergoing Bayesian randomization to 5-day or 10-day decitabine monotherapy showed similar overall response rates and OS) and thus were not able to make formal recommendations about these 2 decitabine regimens. Similarly, although there were some data suggesting superiority of azacitidine to decitabine, we did not find a compelling difference between the 2 drugs, and the panel does not recommend 1 drug over the other.

For Recommendation 4b, 6 RCTs compared low-dose cytarabine monotherapy with low-dose cytarabine combination,[148-150,152,154,161] 3 RCTs compared the effects of azacitidine monotherapy with those of azacitidine combinations[151,157,158] and 1 RCT compared the effects of decitabine monotherapy with a decitabine combination.[160] In addition, 1 observational study compared the effects of lowdose cytarabine combination and hypomethylating agents.[122]

Benefits. The evidence profiles present detailed results regarding how each of the interventions compares to others. Here, we focus on the benefits relevant to the comparisons for which recommendations were made. When azacitidine monotherapy is compared with low-dose cytarabine monotherapy, patients who receive azacitidine monotherapy probably have a lower risk of death over time (HR, 0.81; 95% confidence interval, 0.63-1.04)[64,103] and a lower risk of death at 2 years (risk ratio, 0.78; 95% confidence interval, 0.64-0.94) (moderate-quality evidence). The panel judged that these potential benefits particularly when considering death over time, are minimal. When low-dose cytarabine monotherapy is compared with a low-dose cytarabine combination, patients who received low-dose cytarabine may have a lower risk of febrile neutropenia (risk ratio, 0.51; 95% confidence interval, 0.25-1.03) (low-quality evidence).[150,154,161] The panel considered these benefits small in the context of largely unsuccessful combination partners.

Although the panel considered hypomethylating agents and lowdose cytarabine to be on a par with each other, certain clinical situations exist that might favor the use of 1 of the agents. For patients with adverse disease biology, including complex karyotype, history of myelodysplastic syndromes, and TP53 mutations, hypomethylating agents are favored, as the clinical efficacy of these agents is considered agnostic to adverse biological subtypes of AML. AML with adverse biology is considered resistant to chemotherapy, thus making low-dose cytarabine less favored. Similarly, patients with a recent exposure to hypomethylating agents as treatment of antecedent hematological conditions are not likely to respond to induction with another hypomethylating agent, and cytarabine can be considered in this situation, though rigorous data supporting this approach are lacking.[170]

With regard to combination therapies, low-dose cytarabine-based combination therapies have largely not shown an important benefit compared with low-dose cytarabine monotherapy, and combinations should not be used unless there is evidence through randomized data from large phase 3 trials to support their use. Preliminary reports from the phase 3 VIALE-C trial, in which AML patients considered ineligible for intensive chemotherapy were randomized to low-dose cytarabine vs low-dose cytarabine and venetoclax, show no difference in survival for the combination vs monotherapy (a median of 7.2 months vs 4.1 months, P 5 .11). The combination of low-dose cytarabine and glasdegib was tested in a randomized phase 2 study, with a survival advantage for the combination. However, the relatively small number of patients enrolled in the study makes it difficult to generalize these data. For hypomethylating-based combinations, the compelling data showing high response rates from early-phase trials of venetoclax combined with hypomethylating agents have led to widespread adoption of this regimen. Preliminary reports from the phase 3 VIALE-A study, in which AML patients considered ineligible for intensive chemotherapy were randomized to azacytidine vs azacitidine and venetoclax, report a CR/CRi and an OS advantage to the combination (though no data have been made available at the time of this publication). These guidelines will be updated when data from phase 3 trials are formally reported. **Gemtuzumab ozogamicin has been approved as monotherapy in older patients with AML. However, there are no randomized data comparing it to other monotherapy regimens. The efficacy of gemtuzumab ozogamicin is also limited for patients with adverse disease biology.**

Harms and burden. There was moderate-quality evidence suggesting the likelihood that no important differences in harms exist between azacitidine monotherapy and low-dose cytarabine monotherapy. There was high-quality evidence that decitabine monotherapy results in a higher risk of neutropenia than low-dose cytarabine monotherapy (risk ratio, 1.61; 95% confidence interval, 1.16-2.27) and moderate-quality evidence that it likely results in a higher risk of febrile neutropenia (risk ratio, 1,30; 95% confidence interval, 0.96-1.75). With regard to Recommendation 4a, the panel did not find any harm in choosing 1 regimen over the other and suggests that treatment decisions should be based on disease biology and other factors, as discussed in the previous and next sections. For Recommendation 4b, the majority of data did not favor combination therapies over monotherapy largely due to similar efficacy and the potential for more toxicity.

[…]

Conclusions and research needs for this recommendation.

The panel concluded that there is insufficient evidence of important benefits in choosing between hypomethylating agents and lowdose cytarabine. In addition, **the conditional recommendation for either of the options acknowledges that issues regarding disease biology, patient values and preferences, acceptability, and feasibility are likely to vary importantly across settings and that the balance of potential desirable and undesirable consequences does not favour either treatment approach.**
The panel concluded that there is **insufficient evidence that adding a secondary agent to any of the monotherapies results in an important benefit** and that toxicity and expense need to be weighed when combination regimens are being considered. However, **2 regimens can be considered for combination therapies. Although low-dose cytarabine combined with glasdegib** did demonstrate a moderate survival benefit compared with low-dose cytarabine monotherapy, the unexpectedly low CR rate in the control arm, in addition to the added costs, have to be considered against the potential benefits.
Venetoclax combinations also have been approved by the US Food and Drug Administration for the treatment of older adults with AML. **The panel did not consider these data in depth as part of the recommendations, because results from ongoing randomized trials, with a deeper consideration of toxicities and benefits, are still pending** (azacitidine, clinical trial NCT02993523; cytarabine, clinical trial NCT03069352).
The panel highlighted the **need for additional randomized data regarding less-intensive approaches to treating older patients with AML, particularly for combinations that include agents targeting specific genetic abnormalities.**

Recommendation 5 (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯)

For older adults with AML who achieve a response after receiving less-intensive therapy, the ASH guideline panel suggests continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy.

Hintergrund
Summary of the evidence. We did not find any comparative studies addressing this question in older adults with AML. The panel used 2 sources of indirect evidence to inform the judgments regarding desirable and undesirable effects. First, 2 RCTs compared the outcomes for patients who received less-intensive antileukemic therapy with those for patients who received conventional care, including best supportive care.[64,101] In both studies, patients received at least 6 cycles of azacitidine for 7 consecutive days (each cycle was 28 days). The researchers do not describe how many patients achieved a response after a specific number of cycles (and thus, we could not determine how many cycles beyond response patients received) and report only that, overall, 27.8% of patients achieved a hematologic response (CR or CRi) in 1 study64 and 18% did in the other study.[101]
Second, we conducted a survey among the panel members to systematically collect their experiences. The survey was based on the panelists' best recollection of experiences because it was not feasible to collect information from clinical records given the timelines for the development of these guidelines.
Benefits. Based on the systematic collection of panel members' experience, there is very low certainty evidence that continuing therapy indefinitely may result in longer survival and sustained responses. The difference was estimated to be ;10% in survival up to 2 years. The panel judged that the magnitude of these benefits was moderate.
No study has prospectively demonstrated that continuing less intensive therapy beyond best response ad infinitum provides a survival or quality-of-life advantage over stopping therapy at a defined time point after best response. Continuing less-intensive therapy beyond best response has become a de facto standard of care based, however, on the design of clinical trials in older adults with AML, in which this practice is supported, the noncurative nature of these agents, and the personal experience of providers.
Anecdotally, for patients for whom less-intensive therapy was stopped following CR, relapse occurred shortly thereafter, and reinstitution of the same less-intensive therapy was unsuccessful in re-achieving CR. A survey among panel members reinforced these facts, as almost 100% of members reported continuing therapy until progression or toxicity.
Harms and burden. The collection of the panel members' experience suggested similar proportions of patients and caregivers who are perceived to experience an acceptable burden when continuing treatment.
The panel decided that the potential benefit of continuing therapy beyond best response was sufficient to justify the additional toxicities, costs, and patient and provider burden associated with the additional therapy. However, the panel acknowledged that the potential consequences of continuing therapy were not completely dismissible, estimating in a survey of panel members that 30% of patients would have a poor quality of life and 48% of caregivers would have an unacceptable burden whether therapy continued

indefinitely or was finite, and urged further prospective study of the value of continuing therapy that would include these endpoints.
[…]
Conclusions and research needs for this recommendation.
The panel determined that there is likely to be a net benefit of continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy in older adults with AML who achieve a response after receiving less-intensive therapy. The conditional recommendation places a high value on the potential benefits of survival when therapy is continued indefinitely and on the acceptability of the intervention to clinicians and researchers, who seem to continue therapy as the default option. It also places a lower value on the moderate costs that are likely to result from continuing therapy indefinitely and considers there to be clinical equipoise in quality of life and functional status between these 2 strategies.
[…]
There was general agreement among panel members that **any retrospective study** attempting to show an advantage to continuing therapy indefinitely until progression or toxicity vs stopping therapy at a finite time point **would likely report findings that are unreliable and not valid, as selection bias and confounding by indication for subjects included in each study arm could not be controlled for adequately**.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence we identified for many of the questions. Much of the management of older adults with AML is based on single-arm trials or observational studies. Far more randomized trials have reported results that do not favor 1 approach compared with another than have clearly demonstrated superior outcomes for a new treatment. **As the criteria for data consideration in these recommendations included and prioritized randomized studies over single-arm trials, the panel was limited in supporting certain strategies that have widespread use despite the lack of high-quality data. Consequently, these guidelines could not adequately address the use of certain molecularly targeted agents** in up-front therapy for older adults with AML.

There are **many nuanced or controversial aspects of the management of AML in older adults that were not covered in these guidelines, either due to lack of data to make a formal recommendation, or to the guideline-development process,** in which the panel winnowed down an initial list of 30 potential question to the 6 they felt most important to address.

- Referenzen zu den Empfehlungen dieser LL finden sich im Anhang.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2022) am 31.10.2022

#	Suchfrage
1	[mh “leukemia, myeloid, acute”]
2	acute:ti,ab,kw
3	leu*mia*:ti,ab,kw
4	(myeloid* OR myelogen* OR myeloblast* OR myelocyt*):ti,ab,kw
5	AML:ti,ab,kw
6	#1 OR (#2 AND #3 AND #4) OR #5
7	#6 with Cochrane Library publication date from Oct 2017 to present

Systematic Reviews in PubMed am 31.10.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	leukemia, myeloid, acute[mh]
2	acute[tiab]
3	leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab]
4	myeloid*[tiab] OR myelogen*[tiab] OR myeloblast*[tiab] OR myelocyt*[tiab]
5	AML[tiab]
6	#1 OR (#2 AND #3 AND #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 study[pt] OR validation study[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]

#	Suchfrage
	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 ("2017/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 31.10.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	leukemia, myeloid, acute[mh]
2	acute[tiab]
3	leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab]
4	myeloid*[tiab] OR myelogen*[tiab] OR myeloblast*[tiab] OR myelocyt*[tiab]
5	AML[tiab]
6	#1 OR (#2 AND #3 AND #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 ("2017/10/01"[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]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 31.10.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Anhang

Hintergrundinformationen zu den National Comprehensive Cancer Network Empfehlungen für Erwachsene >=60 Jahre

Not a Candidate for or Declines Intensive Remission Induction Therapy
Treatment options include a clinical trial, or lower-intensity therapy based on the presence or absence of actionable mutations. The preferred regimens include venetoclax combined with HMAs (azacitidine [category 1] or decitabine). Other recommended options include venetoclax combined with low-dose cytarabine [LDAC] or glasdegib combined with LDAC. Patients not considered candidates for combination or targeted therapy may receive monotherapy with HMA (azacitidine or decitabine for either a 5- or 10-day course), GO alone (a category 2B recommendation), or LDAC alone (a category 3 recommendation). Best supportive care with hydroxyurea and transfusion support should also be considered and have been used as the comparator arm in several clinical trials in older unfit patients. For patients with IDH1- or IDH2-mutant AML, preferred treatment options include: ivosidenib or enasidenib for IDH1- or IDH2-mutant AML respectively; or venetoclax-based therapy combined with HMAs (azacitidine [category 1] or decitabine). Other recommended options include venetoclax combined with LDAC or low-intensity therapy with HMAs (azacitidine or decitabine). For patients with FLT3-mutant AML, the preferred treatment option is also venetoclax-based therapy combined with HMAs (azacitidine [category 1] or decitabine). Other treatment options for this category include HMAs in combination with sorafenib and venetoclax combined with LDAC.

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

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- Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

Indikation gemäß Beratungsantrag

Behandlung von erwachsenen Patienten mit einer neu diagnostizierten akuten myeloischen Leukämie (AML), für die eine intensive Chemotherapie nicht geeignet ist

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

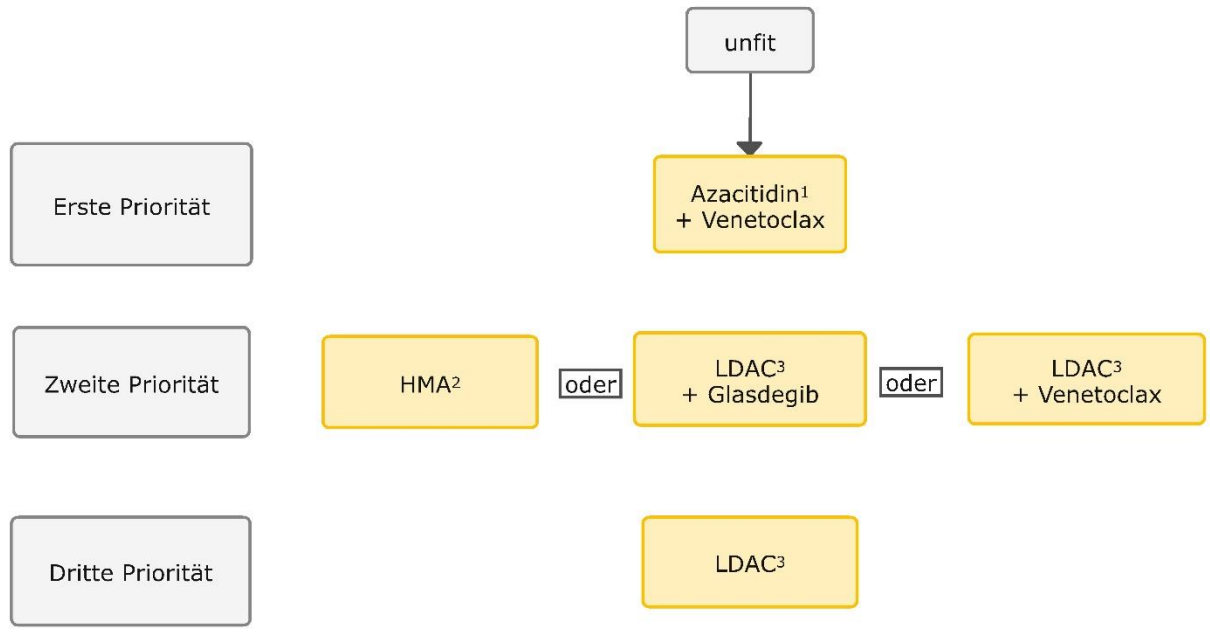
Die Therapie bei nicht intensiv behandelbaren Patientinnen und Patienten (Pat.) mit Erstdiagnose einer AML hat sich mit Zulassung von Venetoclax im Jahr 2021 gewandelt. Standard ist jetzt die Kombination von Venetoclax mit einer hypomethylierenden Substanz. Ebenfalls zum Standard gehört die optimale supportive Therapie (Best Supportive Care, BSC).

Stand des Wissens

Die Akute Myeloische Leukämie (AML) ist eine biologisch heterogene Erkrankung, die unbehandelt in kurzer Zeit zum Tod führt. Die Inzidenz steigt mit dem Alter an. Die Unterteilung der AML erfolgt nach der WHO-Klassifikation anhand zytomorphologischer, zytogenetischer und molekulargenetischer Charakteristika [1]. Therapieentscheidungen werden nach Krankheitsbiologie, Komorbidität und den Therapiezielen der einzelnen Pat. ausgerichtet [2, 3]. Der Therapieanspruch ist bei jüngeren und bei älteren fitten Pat. kurativ.

Ein Therapiealgorithmus für Pat. für die eine intensive Therapie nicht geeignet ist, ist in Abbildung 1 dargestellt.

***Abbildung 1:** Therapie-Optionen für die Primärtherapie unfitter Pat.*



Legende: ——— nicht kurative intendierte Therapie;
[1] bei Kontraindikationen gegen Azacitidin kann Decitabin eingesetzt werden
[2] HMA – hypomethylierende Substanzen
[3] LDAC – niedrig dosiertes Ara-C;

Bei Pat. mit einem biologischen Alter über 75 Jahre oder mit signifikanten Komorbiditäten wie schwerem diabetischem Spätsyndrom, Leber- oder Nierenerkrankungen, Herzinsuffizienz (EF <30%), ECOG ≥3 oder geringen Heilungschancen auf Grund ungünstiger Zytogenetik (unfit, fragil oder frail) besteht das therapeutische Ziel in einer Lebensverlängerung bei möglichst hoher Lebensqualität [4]. Neben BSC soll diesen Pat. eine zytoreduktive ambulante Chemotherapie angeboten werden. Neben einer rein symptomatischen Gabe von Hydroxyurea zur Senkung der Leukozytenzahl wurden in der Vergangenheit die hypomethylierenden Substanzen (HMA) 5-Azacitidin und Decitabin als Monotherapie empfohlen, da sie gegenüber dem historischen Standard von niedrigdosiertem Cytarabin höhere Ansprechraten und eine Überlebensverlängerung bewirken können [5, 6].

Auf Grund der deutlich höheren Wirksamkeit der Kombinationstherapie aus HMA und dem bcl2-Inhibitor Venetoclax wird diese Behandlung der alleinigen HMA-Gabe vorgezogen und ist zum neuen Standard geworden.

Die Kombination von 5-Azacitidin mit Venetoclax führte in einer randomisiert-plazebo-kontrollierten Studie zu einer deutlichen Zunahme der Remissionsraten (CR/CRi) von 28,3% auf 66,4%. Venetoclax verlängerte das Gesamtüberleben in Kombination mit Azacitidin signifikant von 9,6 auf 14,7 Monate. Dieser positive Effekt konnte in allen genetischen Subgruppen nachgewiesen werden [10, 11].

Die Zulassung für die Kombination aus Venetoclax mit einer hypomethylierenden Substanz wurde 2021 von der EMA erteilt. Auf Grund der Datenlage wird diese Kombination als Behandlungsstandard erster Priorität in der Erstlinientherapie nicht intensiv therapierbarer Pat. empfohlen. Für Azacitidin ist die Evidenz robuster, es kann aber von einer ähnlichen Wirksamkeit für Decitabin als Kombinationspartner ausgegangen werden [12].

Kontaktdaten

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Das klinische Management für die Kombinationstherapie mit Venetoclax unterscheidet sich gegenüber dem einer Monotherapie mit HMA deutlich:

Als weitere Option für die Kombination mit LDAC bei unfitten Pat. wurde im Juni 2020 der Hegdehog-Inhibitor Glasdegib zugelassen, der gegenüber einer LDAC-Monotherapie in einer randomisierten nicht Placebo-kontrollierten Studie zu einer Zunahme der CR/CRi-Raten von 5,3% auf 24,3% und zu einer medianen signifikanten Überlebensverlängerung von 4,3 auf 8,3 Monate führte [13]. Einen direkten Vergleich dieser Kombination zur Wirksamkeit von LDAC plus Venetoclax gibt es bislang nicht.

Bei Kontraindikationen gegen HMA oder bei progredienter Erkrankung kann alternativ niedrigdosiertes Cytarabin (LDAC) eingesetzt werden. LDAC hat in dieser Situation eine höhere Wirksamkeit als Hydroxyurea [14].

Ein kleiner Teil von neudiagnostizierten Pat. kann durch leukämiebedingte Organbeeinträchtigung (z.B. leukämische Infiltration der Leber), neutropene infektiöse Komplikationen oder B-Symptome so beeinträchtigt sein, dass bei Erstdiagnose eine intensive Therapie nicht möglich oder vertretbar ist. Durch eine erfolgreiche Behandlung der AML mit HMA oder LDAC, ggf. in Kombination mit Venetoclax kann sich der Zustand so verbessern, dass eine SZT möglich erscheint und erfolgreich durchgeführt werden kann.

Der pU plant folgende spezielle Patientenpopulation zu untersuchen: erwachsene Patienten mit einer neu diagnostizierten akuten myeloischen Leukämie (AML), für die eine intensive Chemotherapie nicht geeignet ist. Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Bei Kontraindikationen oder bei patientenseitiger Entscheidung kann auf eine kausale Therapie verzichtet und eine ausschließlich supportive Therapie durchgeführt werden.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „einer neu diagnostizierten akuten myeloischen Leukämie (AML)“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind oben dargestellt.

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