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: 2023-B-302-z Midostaurin

Stand: November 2023

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

Midostaurin
[neu diagnostizierte akute myeloische Leukämie mit FLT3-Mutation]

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.	Allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach §35a SGB V: - Venetoclax (Beschluss vom 02. Dezember 2021) - Glasdegib (Beschluss vom 18. Februar 2021) - Daunorubucin / Cytarabin (Beschluss vom 22. März 2019) - Gemtuzumab Ozogamicin (Beschluss vom 21. Februar 2019) - Midostaurin (Beschluss vom 5. April 2018) - Decitabin (Beschluss vom 02. Mai 2013) Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie (Stand: 24.06.2023) Arzneimittel, die in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind - Hydroxycarbamid bei chronischer myelomonozytärer Leukämie (CMML).
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**	**Midostaurin** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Midostaurin L01EX10 Rydapt	Erwachsene mit neu diagnostizierter akuter myeloischer Leukämie (AML), die eine Mutation von FLT3 (FMS-like tyrosine kinase 3) aufweisen, in Kombination mit einer Standardchemotherapie mit Daunorubicin und Cytarabin zur Induktion und mit einer Hochdosis-Chemotherapie mit Cytarabin zur Konsolidierung und anschließend als Monotherapie zur Erhaltungstherapie bei Patienten in kompletter Remission.
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.
Cyclophosphamid L01AA01 Endoxan	Konditionierung vor allogener Knochenmarkstransplantation bei: […] akuter myeloischer und akuter lymphoblastischer Leukämie in Kombination mit Ganzkörperbestrahlung oder Busulfan […]
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.
Daunorubicin/Cytarabin (liposomale Formulierung) L01XY01 Vyxeos liposomal	Vyxeos liposomal ist indiziert zur Behandlung von Erwachsenen mit neu diagnostizierter therapieassoziierter akuter myeloischer Leukämie (t-AML) oder AML mit Myelodysplasie-assoziierten Veränderungen (AML-MRC)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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	Entscheidung der Europäischen Komission zur Harmonisierung der Fachinformation von Etopophos: 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)
Gemtuzumab Ozogamicin L01FX02 Mylotarg	MYLOTARG wird angewendet für die Kombinationstherapie mit Daunorubicin (DNR) und Cytarabin (AraC) zur Behandlung von Patienten ab 15 Jahren mit nicht vorbehandelter, neu diagnostizierter CD33-positiver akuter myeloischer Leukämie (AML), ausgenommen akuter Promyelozytenleukämie (APL) (siehe Abschnitte 4.4 und 5.1).
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.
Ivosidenib L01XX62 Tibsovo	in Kombination mit Azacitidin wird angewendet zur Behandlung von erwachsenen Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132- Mutation, die für eine Standard-Induktionschemotherapie nicht geeignet sind

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Midostaurin L01EX10 Rydapt	wird angewendet bei Erwachsenen mit neu diagnostizierter akuter myeloischer Leukämie (AML), die eine FLT3-Mutation aufweisen, in Kombination mit einer Standard-Chemotherapie mit Daunorubicin und Cytarabin zur Induktion und mit einer Hochdosis-Chemotherapie mit Cytarabin zur Konsolidierung und anschließend als Monotherapie zur Erhaltungstherapie bei Patienten in kompletter Remission
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 L01XX52 Venclyxto	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: 2023-B-302-z (Midostaurin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. November 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AML	akute myeloische Leukämie
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CR	complete remission
ECRI	Emergency Care Research Institute
EFS	event-free survival
FLT3-ITD	FMS-like tyrosin kinase3-internal tandem duplication
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GO	Gemtuzumab Ozogamicin
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HMA	hypomethylating agent
HR	Hazard Ratio
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RFS	Relapse-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erwachsene mit neu diagnostizierter akuter myeloischer Leukämie (AML), die eine Mutation von FLT3 (FMS-like tyrosine kinase 3) aufweisen.

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 *akute myeloische Leukämie* 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), 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.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 23.10.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 969 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 10 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

keine

3.2 Systematische Reviews

Pasvolsky et al., 2021 [7].

Maintenance therapy after allogeneic hematopoietic transplant for acute myeloid leukemia: a systematic review and meta-analysis

Siehe auch SR von Gagelmann et al, 2021 [4]; Bewersdorf et al, 2021 [2], Kungwankiattichai et al. [6], Fei et al. [3]

Fragestellung

- To compare the efficacy and safety of maintenance with observation or placebo in patients with AML after allogeneic hematopoietic stem cell transplant (HSCT)

Methodik

Population:

- Patients with AML

Intervention:

- Maintenance therapy after allogenic HSCT
  - Hypomethylating agents (HMAs)
  - Tyrosine kinase inhibitors (TKIs)

Komparator:

- Observation
- Placebo

Endpunkte:

- Primary outcome was overall survival (OS)
- Secondary outcomes:
  - relapse free survival (RFS) defined as time from transplant or from randomization to either AML relapse or death from any cause, whatever occurred first
  - relapse rate
  - safety (including adverse events and graft versus host prophylaxis (GVHD)

Recherche/Suchzeitraum:

- Cochrane Library, PubMed and conference proceedings up to Febuary 2021

Qualitätsbewertung der Studien:

- Cochrane RoB

Ergebnisse

Anzahl / Charakteristika eingeschlossener Studien:

- N=5 RCT

Table 1. Characteristics of included trials.

Study	AML type eligibility criteria	Start of maintenance post transplant (days)	Primary endpoint	Length of follow up (months)	Study drug	Dose and schedule of study drug	Number of patients included	Age (Median, range)	Sex (male, percentage) (%)
Burchert 2020	Flt3-ITD mutated AML	60–100	RFS	42	Sorafenib	PO 800 mg/d¥; for 24 months	43	54 (24–75)	42
					Placebo		40	54 (19–76)	58
Maziarz 2020	Flt3-ITD mutated AML	28–60	RFS	24	Midostaurin	PO 100 mg/d; for 12 months	30	48 (20–61)	53
					SOC		30	56 (20–68)	60
Xuan 2020	Flt3-ITD mutated AML	30–60	relapse rate	21	Sorafenib	PO 800 mg/d¥; till day + 180	100	35 (26–42)	50
					SOC	from transplant	102	35 (26–43)	51
Gao 2020	High risk AML	60–100	relapse rate	28	Decitabine	IV 5 mg/m² on days 1–5,	102	30(3–62)	56
					SOC	every 6–8 weeks; up to 6 cycles§	102	28(2–52)	60
Oran 2020	High risk AML/MDS	42–100	RFS	52	Azacitidine	SC 32 mg/m² for 5 days every	93	57 (19–72)	59
					SOC	4 weeks; for 12 months	94	58 (20–75)	61

AML: acute myeloid leukemia; RFS: relapse free survival; GCSF: granulocyte colony stimulating factor; SOC: standard of care;
MDS: myelodysplatic syndrome; PO: per os; IV: intravenous; SC: subcutaneous.
¥ After dose escalation.
§ patients also received SC rhG-CSF 100 mg/m² on days 0–5 of each cycle.

Table 2. Transplant characteristics of included trials.

Study	Treatment regimen	Number of patients randomized	Remission at transplant		MRD status at transplant		Conditioning regimen		Donor type		
			CHR	No CHR	MRD+	MRD-	MAC	RIC	MSD	MUD	Haplo
Burchert 2020	Sorafenib	43	36	7	27	9	18	25	8	35	0
	Placebo	40	31	9	19	12	19	21	12	28	0
Maziarz 2020	Midostaurin	30	30	0	NA	NA	28	1	10	20	0
	SOC	30	30	0	NA	NA	27	3	15	15	0
Xuan 2020	Sorafenib	100	100	0	NA	NA	100	0	44	8	48
	SOC	102	102	0	NA	NA	102	0	39	6	57
Gao 2020	Decitabine + GCSF	102	92	8	24	68	100	0	20	5	75
	SOC	102	97	5	29	68	102	0	16	13	73
Oran 2020	Azacitidine	93	55	42	NA	NA	73	14	33	44	4
	SOC	94	45	49	NA	NA	75	18	31	53	5

CHR: complete hematological remission; MRD: minimal residual disease; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; Haplo: haploidentical donor; SOC: standard of care; GCSF: granulocyte colony stimulating factor.

Charakteristika der Population:

- N=736 patients in 5 RCTs
- **3 RCT included patients with FLT3-ITD mutated AML (the trials with TKI maintenance),** and two trials included patients with high risk AML, defined as AML with poor genetic abnormalities, primary refractory AML, relapsed AML, or secondary AML in the trial by Gao et al. [12]
- Median age range between 2 and 76 years (*die drei TKI RCTs beinhalten ausschließlich erwachsene PatientInnen*)

Qualität der Studien:

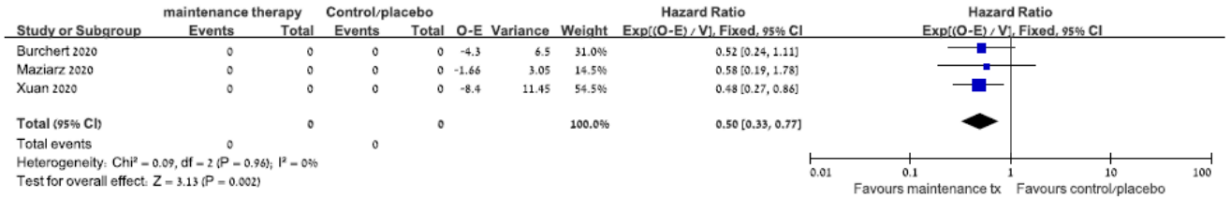
- Three trials were judged at low risk of selection bias [9,11,12]. In the other two trials [7,8], methods of allocation concealment and generation were not reported. Blinding of patients and personnel was done in one trial [9]. All five trials were judged at low risk of attrition bias, and at low risk of reporting bias as clinically important outcomes including overall survival were well addressed

Studienergebnisse:

- **Primary Outcome Overall Survival (OS)**
  - Data from five trials were available for analysis of OS [7–9,11,12]. Maintenance therapy after allogeneic HSCT was associated with an improved OS, OR = 0.61 (95% CI 0.47–0.80, I^2=2%, 547 patients)

- Subgroup analyses by type of maintenance therapy also showed **advantage in OS with either TKI** or HMA maintenance **[HR = 0.50 (95% CI 0.33–0.77, 3 trials, 345 patients, Figure S1)** and HR = 0.69 (95% CI 0.49–0.98, 2 trials, 391 patients, respectively]
- **Survival advantage was observed both in trials in which maintenance was initiated before day +60 post transplant [7,11], as well as trials in which maintenance was initiated after day +60** [9,12] [(HR = 0.50 (95% CI 0.30–0.84, 2 trials, 262 patients) and (HR = 0.47 (95% CI 0.29–0.77, 2 trials, 287 patients), respectively]
- Regarding subgroup analysis by MRD, there was insufficient data to conduct this analysis

Figure·S1.·Overall·survival.·TKI·subgroup·analysis.·¶



Anmerkung: diese Subgruppenanalyse bezieht sich auf die 3 RCTs, die ausschließlich PatientInnen mit FLT3 Mutation beinhalten

- **Relapse-free survival (RFS)**
  - Data from five trials was available for RFS analysis and showed improved RFS in the maintenance group compared with the control arm HR ¼ 0.51 [95% CI 0.40-0.66], 736 patients (Figure 3). Relapse rate was significantly decreased in the maintenance arm compared to the control arm, RR = 0.41 (95% CI 0.20–0.88, 4 trials, 668 patients)
  - Two trials reported RFS according to MRD status. In the SORMAIN trial, **patients who were MRD negative prior to transplant benefited most from maintenance therapy in terms of RFS: none of the MRD negative patients in the maintenance arm relapsed or died during follow up, whereas 5 of 12 MRD negative patients in the placebo arm relapsed (p=0.028) [9].** Similarly, in the trial by Gao et al., patients with MRD negativity had the most benefit from maintenance therapy: there was a 2 year cumulative relapse rate of 5.9% in the MRD negative maintenance arm versus 31% in the MRD negative no-maintenance arm (HR 0.16, p<0.01). The difference in relapse rate was less pronounced if the MRD was positive prior to transplant, with relapse rates in the maintenance and no-maintenance arms of 34.5 and 52.9%, respectively (HR 0.48, p=0.05) [12]

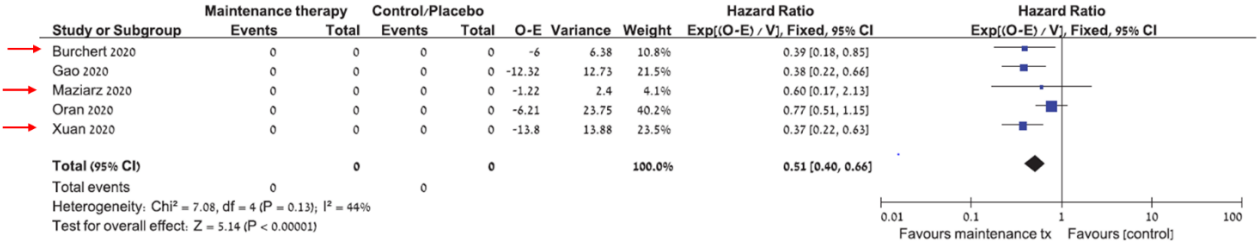


Figure 3. Relapse free survival of patients treated with post-transplant maintenance compared to no maintenance. CI: confidence interval; O: observed; E: expected.

→ Studien mit PatientInnen mit FLT3-mutierter AML

- **Adverse Events**
  - Three trials reported grade 3 or 4 adverse events. The risk of any grade 3 or 4 adverse events did not increase with the addition of maintenance after allogeneic HSCT, RR = 1.0 (95% CI 0.83–1.20, 464 patients).

- **Acute/chronic graft versus host prophylaxis GVHD**
  - No difference was noted between the two arms regarding grade 2–4 acute GVHD, mild-moderate chronic GVHD or severe chronic GVHD

- **Infections**
  - There was no difference between the maintenance and control arms in the rate of all infections or grade 3 or 4 infections [(RR = 0.98 (95% CI 0.83–1.16, I^2=0%, three trials, 585 patients) and (RR = 0.96 (95% CI 0.68–1.36, three trials, 464 patients), respectively].

- **Hematological toxicity**
  - There was no difference between the two arms in grade 3 or 4 thrombocytopenia or in grade 3 or 4 neutropenia.

Anmerkung/Fazit der Autoren

- In conclusion, our meta-analysis shows that post-transplant maintenance therapy in AML patients is effective in decreasing relapse rate and improving RFS and OS, with a satisfactory safety profile.

Referenzen (RCTs):
[7] Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. Bone Marrow Transplant. 2021;56(5):1180–1189.
[8] Oran B, de Lima M, Garcia-Manero G, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. Blood Adv. 2020;4(21): 5580–5588.
[9] Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). J Clin Oncol. 2020;38(26):2993–3002.
[11] Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. Lancet Oncol. 2020;21(9): 1201–1212.
[12] Gao L, Zhang Y, Wang S, et al. Effect of rhG-CSF combined with decitabine prophylaxis on relapse of patients with high-risk MRDnegative AML after HSCT: an open-label, multicenter, randomized controlled trial. J Clin Oncol. 2020;38(36):4249–4259.

Kommentare zum Review

- Die Wirkstoffe Midostaurin und Sorafenib sind im vorliegenden Anwendungsgebiet nicht zugelassen
- **Für den Wirkstoff Midostaurin wurde eine Studie inkludiert, diese zeigte keine Wirksamkeit für OS und RFS in dieser Therapiephase**
- Das Verzerrungspotential wird nur für einzelne Domänen angegeben, eine Gesamteinschätzung auf Studienbasis fehlt
- Daten zu den Safety Endpunkten sind nur unzureichend berichtet. Es ist unklar, aus welchen der 5 RCTs die Daten stammen
- 2 weitere SRs mit Meta-Analysen, die neben Daten aus RCT auch Daten aus Beobachtungsstudien berücksichtigen, bestätigen die Ergebnisse zur Wirksamkeit von TKI als Gesamtgruppe in dieser Therapiephase[2,4]

Guo Y et al., 2022 [5].

Efficacy and safety of adding gemtuzumab ozogamicin to conventional chemotherapy for adult acute myeloid leukemia: a systematic review and meta-analysis

PROSPERO: CRD42020190386

Fragestellung

meta-analysis to compare whether the addition of GO to standard chemotherapy in AML improves its efficacy and safety, as well as to determine the optimal dose and treatment phase of GO in combination

Methodik

Population:

- patients had de novo or secondary untreated AML or entered complete remission (CR) after induction chemotherapy

Intervention:

- adding GO to conventional chemotherapy

Komparator:

- conventional chemotherapy alone

Endpunkte:

- overall survival (OS), relapse-free survival (RFS), CR with or without incomplete platelet recovery, relapse risk and resistant disease, and safety end points

Recherche/Suchzeitraum:

- Nov. 2021, MEDLINE, Embase, Web of Science, Cochrane Library

Qualitätsbewertung der Studien:

- RoB 2.0, GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 RCTs (N=6.333)

Charakteristika der Population/Studien:

- Induktionsphase: 2 RCTs
- Induktion und Post-Remissionsphase: 5 RCTs
- Konsolidierungsphase: 1 RCT
- Post-Remissionsphase: 2 RCTs

Qualität der Studien:

- All included trials were open-label randomized trials, and two of the studies [14,15] were classified as high risk due to large gaps in the number of patients deviating from the intended intervention.

Studienergebnisse:

- OS: kein signifikanter Unterschied zwischen den Studienarmen (7 RCTs)
  - Subgruppe mit 3mg/m^2 single-dose: HR 0.89, 95% CI: 0.81–0.99, p = 0.03, I^2=0% (2 RCTs) zugunsten GO plus Chemotherapie
  - Subgruppe patients with favorable cytogenetic: HR 0.50, 95% CI: 0.28–0.89, p = 0.02), I^2=43% (3 RCTs) zugunsten GO plus Chemotherapie
- RFS: HR 0.84, 95% CI: 0.73–0.98, p = 0.02, I^2=45% (6 RCTs) zugunsten GO plus Chemotherapie
  - Subgruppe mit 3mg/m^2 single-dose: HR 0.85, 95% CI: 0.76–0.96, p = 0.007, I^2=0% (2 RCTs) zugunsten GO plus Chemotherapie
  - Subgruppe mit 3 mg/m^2 fractionated schedule HR 0.52, 95% CI: 0.36–0.76, p = 0.0007 (1 RCT) zugunsten GO plus Chemotherapie
- CR: kein signifikanter Unterschied zwischen den Studienarmen (8 RCTs)
- relapse risk: OR 0.78, 95% CI: 0.68–0.91, p = 0.001, I^2=0% (7 RCTs) zugunsten GO plus Chemotherapie
  - Subgruppe mit 3 mg/m^2 fractionated schedule OR 0.48, 95% CI: 0.28–0.84, p = 0.01 (1 RCT) zugunsten GO plus Chemotherapie
- incidence of resistant disease: OR 0.72, 95% CI: 0.61– 0.84, p < 0.0001, I^2=24% (7 RCTs) zugunsten GO plus Chemotherapie
  - Subgruppe flat dose of 5 mg GO plus induction chemotherapy compared with those given induction chemotherapy alone: OR 0.53, 95% CI: 0.37–0.76, p = 0.0006 (1 RCT)

Anmerkung/Fazit der Autoren

In summary, adding low-dose and fractionated schedule of GO to conventional chemotherapy has a favourable benefit/risk ratio for newly diagnosed de novo or secondary adult AML.

Wen B et al., 2020 [9].

Indirect comparison of azacitidine and decitabine for the therapy of elderly patients with acute myeloid leukemia: a systematic review and network meta-analysis.

Fragestellung

A systematic review and network meta-analysis were performed to indirectly compare the efficacy and safety of decitabine and azacitidine in elderly AML patients.

Methodik

Population:

- elderly AML patients

Intervention/Komparator

- azacitidine or decitabine, and compared the two drugs against each other, or compared them to standard supportive care, or placebo

Endpunkte:

- mortality, complete and partial responses, and haematologic improvement

Recherche/Suchzeitraum:

- PubMed, Medline, Web of Science, EMBASE and Cochrane Library through May 14, 2019.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

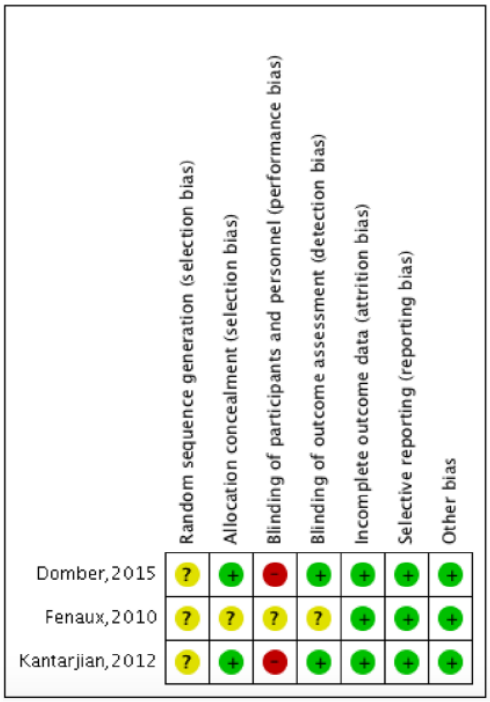
- 3 RCTs
  - Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010;28(4):562–9.
  - Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts. Blood. 2015;126(3):291–9.
  - Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2012;30(21):2670–7.

Charakteristika der Population:

- Pat. die nicht für SZT geeignet sind (Alter, ECOG, Risikofaktoren), Induktionstherapie
- The three RCTs involved a total number of 1086 patients with an age range of 64–91 years old. Two RCTs compared of azacitidine (75 mg/m2/day, SC × 7 days) and the conventional care regimens (CCR), including lowdose cytarabine (LDAC) or best supportive care (BSC) or intensive chemotherapy (IC), and included 601 patients (296 azacitidine and 305 CCR; age average 74; range 64–91 years old). The other RCT compared decitabine (20 mg/m2, IV, QD × 5 days/4 weeks) to the CCR including

supportive care or cytarabine and included 485 patients (242 decitabine and 243 CCR; age average 73; range 64–91 years old).

Qualität der Studien:



Studienergebnisse:

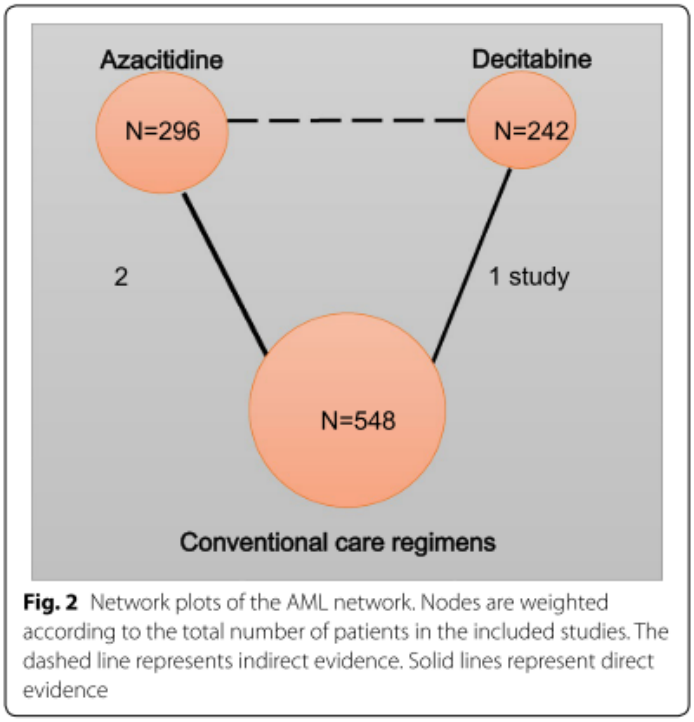


Fig. 2 Network plots of the AML network. Nodes are weighted according to the total number of patients in the included studies. The dashed line represents indirect evidence. Solid lines represent direct evidence

- Direct comparisons showed that azacitidine significantly reduced mortality (RR = 0.90, 95% CI 0.83–0.98, $p < 0.001$, $I^2 = 94.0\%$), while decitabine did not show improvement in mortality rates compared to CCR (RR = 0.97, 95% CI 0.92–1.02). Higher complete responses were reported in both groups as compared to CCR.

- Indirect head-to-head comparisons showed that azacitidine significantly reduced the mortality rate (RR = 0.83 95% CI 0.77–0.90, I2 = 82.8%) and anemia (RR = 0.68, 95% CI 0.52–0.90, I2 = 82.2%). Patients in the azacitidine group were more likely to achieve complete response (CR) compared to decitabine (RR = 1.66, 95% CI 1.17–2.35, I2 = 65.3%, low certainty). There was no statistically significant difference found in other study outcomes including partial response rate, neutropenia and thrombocytopenia. Similarly, azacitidine showed improved overall survival by SUCRA analysis compared to decitabine (74.7% vs. 47.1%).

Anmerkung/Fazit der Autoren

Compared to CCR, azacitidine or decitabine yields both better outcomes, including mortality, overall response, and improvement of haematological parameters. For indirect head-to-head comparisons, low certainty of evidence was found when comparing azacitidine and decitabine. The superiority of either agent cannot be confirmed in this study and head-to-head clinical trials are still required to provide more information about the efficacy and safety of the two agents. In addition, other factors including adverse effects, patient preferences and cost, are also important and should be taken into consideration in the final choice between the two agents.

Kommentare zum Review

- The consistency of the network could not be evaluated because there were no closed loops
- Heterogeneity and publication bias could not be obtained because of the small number of trials investigating each agent
- direct and indirect head-to-head comparisons were performed with low or moderate of the certainty of the evidence
- Subgroup analysis could not be assessed due to the paucity of data. → unklar ob Patienten vorbehandelt oder nicht.

Zhang RJ et al., 2021 [10].

Hypomethylating agents for elderly patients with acute myeloid leukemia: a PRISMA systematic review and meta-analysis

Fragestellung

to evaluate the efficacy of HMAs and their adverse effects when treating older AML patients

Methodik

Population:

- patients aged ≥55 years, with morphologically proven diagnosis of AML and with no previous allogeneic stem cell transplantation, first-line setting

Intervention:

- HMA (u.a. Azacitidin, Decitabin)

Komparator:

- conventional care regimens (CCR) including best supportive care (BSC), low-dose cytarabine or intensive chemotherapy

Endpunkte:

- CR, OS, AEs

Recherche/Suchzeitraum:

- Juli 2020, PubMed, Embase, Cochrane Central Register of Controlled Trials

Qualitätsbewertung der Studien:

- Cochrane RoB

Ergebnisse

Anzahl eingeschlossener Studien:

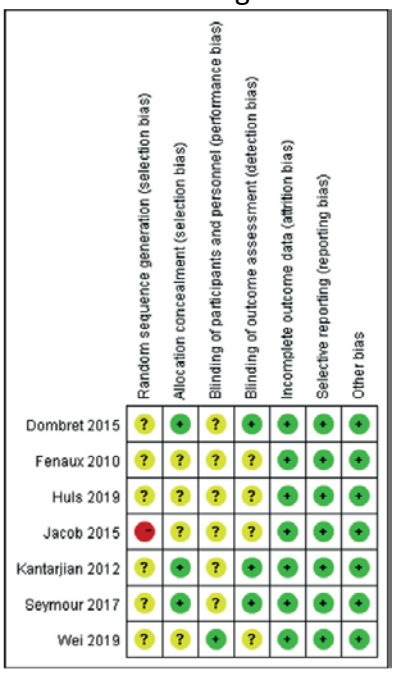
- 7 RCTs, davon 5 Phase III (N=1.674), 2 Phase II (N=292)

Charakteristika der Population/Studien:

- Medianes Alter zwischen 62 und 76 J.

Qualität der Studien:

- Alle Studien mit unklarem oder hohem RoB; u.a. nur 1 RCT doppelt-verblindet, unklare Randomisierung



Studienergebnisse:

- OS:
  - Azacitidin vs. Standard: HR 0,73 (95%-CI 0,64;0,83), p<0,00001, I^2=29% (5 RCTs)
  - Decitabin vs. Standard: HR 0,82 (95%-CI 0,68;0,98), p=0,03, I^2=0% (2 RCTs)
- CR:
  - HMA vs. Standard: RR 1,46 (95%-CI 1,08;1,99), p=0,006, I^2=69% (6 RCTs)
- Neutropenie:
  - HMA vs. Standard: RR 1,30 (95%-CI 1,07;1,59), p=0,008, I^2=43% (6 RCTs)

Anmerkung/Fazit der Autoren

HMAs showed improved response rates and OS in comparison to CCR or placebo. Although HMAs are associated with a higher incidence of AEs such as neutropenia, thrombocytopenia, and pneumonia, demethylation drugs were well-tolerated in the treatment of elderly AML.

3.3 Leitlinien

Sekeres MA et al, 2020 [8].

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 1 (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯)

For older adults with newly diagnosed AML who are candidates for such therapy, the American Society of Hematology (ASH) guideline panel ***recommends offering antileukemic therapy over best supportive care.***

Hintergrund:
A total of 15 studies were included in the evidence syntheses regarding benefits and harms for identified health outcomes.[62,64,85-97] Eighteen additional studies were reviewed but excluded from the meta-analyses due to lack of data on the outcomes prioritized by the expert panel.98-116 Given the challenges in randomizing patients to intensive or less-intensive treatments, most of the included studies were observational.[62,85,86,93,95,96] Two were randomized clinical trials (RCTs).[94,96] One study was an RCT64 in which patients were preselected by their physicians as appropriate candidates for either intensive therapy, less-intensive therapy, or best supportive care and then randomized to their preselected conventional-care treatment or to azacitidine. Within this study, patients preselected for less-intensive therapy and then randomized to receive azacitidine or best supportive care were used for RCT data in our analyses. Data from the same study comparing intensive therapy vs best supportive care were considered observational, as patients did not undergo a formal randomization to receive best supportive care vs intensive therapy. Eleven studies, all classified as observational, addressed the comparison between intensive antileukemic therapy and best supportive care.[62,64,85-93] These studies provided evidence for mortality and serious adverse events. Ten studies addressed the comparison between less-intensive antileukemic therapy and best supportive care.[62,64,88-90,92,94-97] These studies provided evidence for mortality, hospitalization, and serious adverse events. The EtD framework for this recommendation is available online at https://guidelines.gradepro.org/profile/Lfz8s2r0kpE and https://guidelines.gradepro.org/profile/Uiwz0FeE2z8.
Benefits. The panel judged that antileukemic therapy, compared with best supportive care, provides a benefit. For the comparison between intensive antileukemic therapy and best supportive care, low-quality evidence suggests that the hazard of death for patients who receive intensive antileukemic therapy may be 0.36 times that of the patients who receive best supportive care, over time (HR, 0.36; 95% confidence interval, 0.26-0.50).62,64,85-93 Low-quality evidence suggests that the risk of death for patients who

receive intensive antileukemic therapy may be lower than that of the patients who receive best supportive care at 30 days,[62,88,89,92,93] at 6 months,86,91 and at 1 year64,86,87,90-92 (relative risk [RR] [95% confidence interval], 0.28 [0.14-0.58] at 30 days, 0.57 [0.45-0.72] at 6 months, and 0.69 [0.60-0.80] at 1 year).

For the comparison between less-intensive antileukemic therapy and best supportive care, moderate-quality evidence from randomized clinical[64,94,97] trials and low-quality evidence from observational studies62,96 suggests the likelihood of a lower risk of death over time for patients who receive less-intensive antileukemic therapy than in those who receive best supportive care (HR [95% confidence interval], 0.74 [0.60-0.91] for randomized trials and 0.22 [0.16-0.29] from observational studies). Very low-quality evidence suggests that the risk of death of patients who receive less-intensive antileukemic therapy compared with that of patients who receive best supportive care may be lower at 30 days62,88,89,92 (RR, 0.45; 95% confidence interval, 0.25-0.81), and moderate-quality evidence suggests that it is likely lower at 6 months94,95 (RR, 0.76; 95% confidence interval, 0.63-0.92) and 1 year64,94 (RR, 0.85; 95% confidence interval, 0.77-0.94). The studies not included in the meta-analyses[98-115] reported outcomes similar to those described herein.

With consideration of the quality of evidence and the thorough meta-analysis, the data presented herein confirm what many practitioners, if not patients, know from experience: that **any therapy is better than no therapy if the goal is prolongation of life, even in an older, less "fit" patient cohort.**[117] These studies and others demonstrate that with careful consideration by providers regarding patients' tolerance of more- or less-intensive therapy, treatment beyond best supportive care extends survival of older AML patients. In fact, the principal cause of death in this population, even in older subjects, is disease rather than treatment-related mortality[118] or noncancer mortality. For the observational studies, the panel acknowledges the likely selection bias that contributed to benefits for those patients receiving antileukemic therapy compared with those receiving best supportive care. The panel also recognizes that the definition of a "candidate" for such therapy includes a thorough understanding and acknowledgment of patient goals.

Harms and burden. For the comparison between intensive antileukemic therapy and best supportive care, low-quality evidence suggests that the risk of febrile neutropenia is likely higher with intensive antileukemic therapy than with best supportive care64 (RR [95% confidence interval], 1.13 [0.57-2.21]). For the comparison between less-intensive antileukemic therapy and best supportive care, very low-quality evidence suggests that there may be an increased risk of febrile neutropenia and pneumonia with less-intensive antileukemic therapy. Low-quality evidence suggests that hospitalization may be 2 days longer, on average, when patients receive less-intensive antileukemic therapy rather than best supportive care.[90] In addition, patients who receive antileukemic therapy may experience more burden related to how the treatment is administered, particularly the intensive antileukemic therapy.

Contextualizing the ramifications of treatment is a critical part of the physician role in chemotherapy consent. Many patients approach therapy with apprehension, keeping in mind the classical toxicities of treatment like nausea, infection, and bleeding. These analyses demonstrate that for patients receiving either intensive or lessintensive therapy, treatment may be associated with higher rates of febrile neutropenia and hospitalizations. This finding is consistent with data showing that, even for patients with pancytopenia, severe neutropenia accompanies antileukemic therapy when either intensive or less-intensive agents are used. However, the analyses show that the magnitude of additional harm attributable to therapy is small. Such information should inform conversations with patients.

Patients who choose to be treated need to know that hospitalization or complications of therapy at some point, even with less intensive treatment, is more likely. Though the increase in risk may be small given the inherent complications of untreated disease, careful consideration of patient comorbidities, values, and resources should guide treatment decision-making.

Protocols for the prevention and management of febrile neutropenia largely derive from patients treated intensively but are applicable to patients receiving less-intensive treatment given the validity of similar management of the same underlying disease with the same degree of adverse event, even with different provoking factors. The panel acknowledges that in unblinded studies, patients receiving antileukemic therapy and best supportive care may have also received differential management of complications, including recommendation for hospitalization.

Other EtD criteria and considerations. Three studies addressed patients' values and preferences regarding the outcomes of interest.[116,119,120] These showed that patients placed a high value on achieving CR (health state median, 0.70, on a scale from 0 to 1, where 0 is dead and 1 is totally healthy)116 and consider relapse an outcome with a negative value (health state and utility ranged from 0.10 to 0.50 across studies).116,119,120 The panel judged that patients are likely to place a high value on the potential benefits of the treatment, as well as on being offered treatment when there is no certainty about the benefits. […]

Recommendation 2 (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯)

For older adults with newly diagnosed AML considered candidates for intensive antileukemic therapy, the ASH guideline panel ***suggests intensive antileukemic therapy over less-intensive antileukemic therapy.***

Hintergrund

Summary of the evidence. There were 20 studies addressing this question, reported in 21 publications,[54,62,64,76,80,90,92,101,104,121-132] the majority of which were observational.[54,62,76,80,90,92,101,104,121-132] One study was an RCT[64] in which patients in the standard-of-care arm were preselected by their physicians to receive either intensive (induction) therapy, less-intensive therapy, or best supportive care, vs less-intensive therapy with azacitidine. For this study, for outcomes in which the researchers presented data comparing intensive therapy to azacitidine among patients preselected for intensive therapy, we used this as RCT data. For outcomes in which all standard of care was combined, we used data as observational.
Studies provided data about mortality, allogeneic hematopoietic stem cell transplantation, serious adverse events, and hospitalization.

Benefits. Very low-quality evidence suggests that patients who receive intensive antileukemic therapy may be at lower risk of death than those who receive less-intensive antileukemic therapy, over time (HR, 0.78; 95% confidence interval, 0.69-0.89).[62,80,90,101,104,121,124,125,129,132]

Very low-quality evidence suggests that the risk of death may also lower at 1 year (risk ratio, 0.93; 95% confidence interval, 0.85-1.01).[54,62,76,90,92,104,121,123,127-129,132] Low-quality evidence suggests the likelihood that patients who receive intensive antileukemic therapy are 6.6 times more likely to receive an allo-HSCT than those who receive less-intensive antileukemic therapy (risk ratio, 6.65; 95% confidence interval, 4.13-10.71).

Very low-quality evidence suggests that, counterintuitively, those who receive more-intensive antileukemic therapy may be less likely to have pneumonia (RR, 0.25; 95% confidence interval, 0.06-0.98) than those receiving less-intensive therapy, up to 2 years.[64] The panel was limited by the lack of randomized data addressing this critical question of whether older patients considered fit for chemotherapy actually have outcomes superior to those of similar patients receiving less-intensive therapy. Historically, treatment of older adults with AML involved a subjective determination of whether a patient was considered fit for intensive chemotherapy, and if the patient was considered fit, the recommendation was generally to proceed with intensive chemotherapy. Although fitness is still a major factor driving initial treatment recommendations, the consideration for intensive chemotherapy over a less-intensive regimen includes a more holistic assessment of the most appropriate induction regimen and is driven by the physician's assessment of disease and patient characteristics and by an analysis of patient goals in the context of anticipated outcomes with each treatment approach. For example, patients with certain adverse molecular characteristics, such as a TP53 mutation, may not be offered intensive chemotherapy out of a belief by treating physicians that it is not likely to benefit these patients more than less-intensive approaches, such as hypomethylating agents.[133]

Although those who receive more-intensive antileukemic therapy are more likely to proceed with stem cell transplant than those who receive less-intensive therapy, the difference may be due to factors influencing the decision regarding initial treatment rather than a higher success rate with intensive chemotherapy, although a higher efficacy (eg, remission) enabling transplant is quite possible.

Newly approved therapeutic approaches, including hypomethylating agents combined with venetoclax as well as targeted therapies, may increase the efficacy of less-intensive therapies (but may also increase their intensity) and thus mandate a reexamination of this question.[134] The seemingly paradoxical lower death rate, cumulative lower adverse events, and lower pneumonia rates with intensive chemotherapy from 1 study may be due to a more common, faster, or more complete return to normal hematopoiesis than was achieved with formerly (but not necessarily currently) available nonintensive therapies.

Harms and burden. Very low-quality evidence suggests that patients who receive intensive antileukemic therapy may be more likely to experience treatment-emergent adverse events, particularly during the induction phase of therapy (RR, 1.34; 95% confidence interval, 1.03-1.75),[79] and to be hospitalized for longer (mean difference, 6.84 days; 95% confidence interval, 3.44-10.24)[76] than patients who receive less-intensive antileukemic therapy. Patients who receive intensive antileukemic therapy must receive it in the hospital, which is a burden to the patients and the system compared with less-intensive antileukemic therapy.

Insofar as nonintensive chemotherapy can be administered more often in the outpatient setting, it is expected that intensive chemotherapy, with its attendant myelosuppression and gastrointestinal toxicity

requiring hospitalization, would lead to a longer time in the hospital. Moreover, many patients given nonintensive chemotherapy would not be considered intensive care unit (ICU) candidates based on personal goals of care. However, exposure to intensive chemotherapy tends to be brief compared with the indefinitely repetitive cycles of nonintensive therapy. Such ongoing therapy may be difficult for patients to tolerate psychologically, physically, and financially.
[…]
Conclusions and research needs for this recommendation.
The panel determined that there may be a net benefit of intensive antileukemic therapy over less-intensive antileukemic therapy in older adults with AML who are candidates for intensive antileukemic therapy. This recommendation places a high value on the potential benefits of intensive over less-intensive antileukemic therapy. Even though there is low to very low-quality evidence of such benefits, there is no higher-quality evidence that less-intensive antileukemic therapy results in better health outcomes. Although values and preferences are likely to vary, it is likely that most patients value the uncertain benefits more than the uncertain harms. […]
The evidence includes patients with both intermediate and poor prognosis. Because of the way in which studies are reported, we could not separate these subgroups. Even though at the study level there seem to be no differences in outcomes between them, the panel believes that studies that explore this issue at the patient level (randomized controlled trials and observational studies with proper subgroup analyses and systematic reviews with individual patient data) may help inform this question when these recommendations are revised and updated.
Finally, the panel felt strongly that use of **potentially more efficacious combination therapies that may be less intensive than traditional, "3 1 7" cytotoxic therapy, particularly those based on the addition of venetoclax, could alter these conclusions.** However, supportive randomized data are not currently available, and the addition of new agents may increase the toxicity of so-called nonintensive therapies. The panel advocated for future research priorities focusing on better determination of "fitness" for intensive chemotherapy, as **the panel could not clearly define a patient population "unfit" for intensive chemotherapy, despite models that have been developed to help in this determination**.

Recommendation 3 (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯)

For older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allogeneic hematopoietic stem cell transplantation (HSCT; allo-HSCT), the ASH guideline panel suggests postremission therapy over no additional therapy.

Remarks: In some settings, patients may receive 2 cycles of intensive antileukemic therapy even if they achieve remission after the first one. In those settings, the panel considered the second cycle of intensive therapy to be postremission therapy.

Hintergrund
Twelve studies addressing different postremission therapy strategies informed this question. In 2 studies, researchers compared no postremission therapy to 1 cycle of consolidation therapy (evidence profile 1). One was a RCT in which researchers reported mortality and time to recurrence in 297 participants,[138] and another was an observational study in which researchers reported time to recurrence in 132 participants.[139] In 1 observational study, researchers reported the outcomes for 48 patients who received 1 cycle of consolidation plus 1 cycle of postremission therapy with gemtuzumab ozogamicin or 1 cycle of consolidation therapy plus autologous HSCT (auto-HSCT; evidence profile 2).[140]
In 4 studies, 3 RCTs with 258 participants[70,141,142] and 1 observational study with 126 patients,106 researchers compared mortality and time to recurrence between patients who received 2 cycles of consolidation therapy and patients who received 1 cycle (evidence profile 3). In 1 RCT, researchers compared the outcomes of 6 cycles of ambulatory postremission therapy vs those of 1 cycle of consolidation therapy in 164 participants (evidence profile 4).[66] In 1 RCT, researchers compared 3 cycles of postremission therapy with those of 2 cycles of consolidation plus auto-HSCT in 25 participants (evidence profile 5).[143] In 1 RCT, researchers compared 3 cycles of postremission therapy with gemtuzumab ozogamicin vs no therapy in 232 participants (evidence profile 6).[144] In 2 observational studies, researchers compared auto-HSCT vs no therapy in 503 patients (evidence profile 7).[145,146]
Benefits. Patients who receive more postremission therapy seem to do better than patients who receive less postremission therapy. There is moderate-quality evidence that patients who receive 1 cycle of consolidation have lower mortality (RR, 0.96; 95% confidence interval, 0.89-1.03), have a longer survival

time by a median of 3 months and a longer time to recurrence by a median of 1 month than patients who do not receive consolidation.[138]
Low-quality evidence suggests that patients who receive 6 months of low-dose outpatient ambulatory postremission therapy may have 0.63 times the risk of dying (95% confidence interval, 0.64-1.07) and moderate-quality evidence of borderline significance suggests that they have 0.66 times the risk of recurrence (95% confidence interval, 0.44-1) than people who receive 1 cycle of intensive inpatient consolidation therapy. There is also moderate-quality evidence that the risk of febrile neutropenia is lower with 6 cycles of low-dose outpatient ambulatory postremission therapy (RR, 0.39; 95% confidence interval, 0.30-0.52).[66]
Low-quality evidence suggests that patients who do not receive postremission therapy may have higher mortality than those who receive 3 cycles of gemtuzumab ozogamicin (RR, 1.05; 95% confidence interval, 0.89-1.24).[144] Very low-quality evidence suggests that patients who do not receive consolidation therapy may have a higher risk of death (RR, 1.75; 95% confidence interval, 0.96-3.20) and a higher risk of recurrence (RR, 2.24) than patients who receive auto-HSCT.[145,146]
Although the data demonstrate that postremission therapy is of modest benefit for older patients who achieve CR following intensive induction chemotherapy, the best postremission strategy, in terms of both the chemotherapy regimen and treatment duration, remains to be determined. The use of allogeneic hematopoietic cell transplantation as a postremission curative therapy in older patients has increased with the development of reduced-intensity conditioning regimens, but no RCTs have compared this treatment modality to chemotherapy in older adults. This treatment modality, however, is used in a minority of patients, whereas the majority of older patients receive either chemotherapy or no postremission treatment, leaving open the question of relative efficacy. The greater part of research efforts to date related to older adults with AML has been directed at improving the induction strategy and the identification of novel agents and their addition to low-intensity or high-intensity therapy. The panel considers it a priority and an opportunity to design and conduct clinical trials that will identify the best postremission strategy/strategies.
Harms and burden. Very low-quality evidence suggests the possibility of greater harms of more postremission therapy than less postremission therapy. In addition, patients who receive more postremission therapy have the additional burden of such therapies. The panel recommends that in addition to discussions with patients regarding prolonging survival and treatment-related mortality associated with any postremission modality, decisions about postremission treatment should include the patient's expectations in relation to the intensity of postremission therapy, the patient's social circumstances, the impact on the patient's quality of life, and the availability of family support.
Conclusions and research needs for this recommendation.
[…] The panel acknowledged that **the evidence is not sufficient to make a recommendation for a specific number of cycles beyond 1 cycle.** It is likely that there is little variability among patients in the value of prolonged survival and remaining in remission for a longer time. Postremission therapy is likely to be accepted by all stakeholders. The panel also recognized that maintenance therapy with a hypomethylating agent may be an alternative to or improvement over traditional consolidation therapy, based on a recent randomized study showing a survival advantage to a maintenance hypomethylating agent following intensive, induction chemotherapy.[147]
The panel highlighted the unmet need for well-conducted prospective and standardized research to inform this recommendation. **The definition of "postremission" and the therapy regimens vary considerably across settings,** which was reflected in the studies used to inform this recommendation. […]

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

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

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

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.96 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**.

Recommendation 6 (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯)

For older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life care or hospice care), the ASH guideline panel suggests having red blood cell (RBC) transfusions be available over not having transfusions be available There may be rare instances where platelet transfusions may be of benefit in the event of bleeding, but there are even less data to support this practice and it is anticipated that platelet transfusions will have little or no role in endof-life or hospice care.

Hintergrund

We did not find any comparative studies addressing this question in older adults with AML. The panel decided to use indirect evidence, obtained from 2 published systematic reviews of the literature, neither of which was focused on older adults with AML, to inform this question.[163,164] The first systematic review focused on the effects of RBC transfusions for patients receiving palliative care.[163] The mean age of patients included in the studies ranged from 64 through 70 years, and it was specified (only in some of the studies) that the patients had terminal malignancies or advanced nonmalignant disease.

The second systematic review focused on the effects of transfusions, both RBC and platelets, in palliative-care patients with cancer.[164] The authors described the outcomes for patients of all ages, with hematological malignancies and solid tumors. The outcomes of interest were measured in different ways across studies and therefore could only be summarized narratively. For most of these outcomes, there are only noncomparative data, given that most of the studies included in both systematic reviews were case series.

Benefits. The evidence about benefits was obtained from case series of patients receiving RBC transfusions. Very low-quality evidence suggests that the median or mean survival after transfusion may range from 42 days to 3 months; however, 3 of the 4 studies reported a time of ,50 days. There is also very low-quality evidence that transfusions may yield an improvement in well-being scores. One study reported a change from 4.2 to 5.8 and another from 3.9 to 6.0 (measured using a 10-point visual analog scale, with higher scores reflecting improved well-being). The proportion of patients for whom an improvement in well-being was reported (by the patients themselves or the clinicians) was 65% in 1 study and 51.4% in another. Finally, there is very low-quality evidence that 70% of patients may perceive an improvement in fatigue after transfusion. The panel judged that the magnitude of these benefits was moderate.

In addition to potential improvements in well-being and fatigue, the panel determined that 1 of the most important reasons to allow transfusions for older adults with AML who are no longer receiving antileukemic therapy is that it may help facilitate timely hospice enrollment for the transfusion dependent, as many hospice programs do not allow transfusions. Moreover, the lack of evidence that such transfusions prolong life for patients at this stage argues that for patients who experience quality-of-life benefits, they are palliative and not disease focused.

Harms and burden. The studies did not measure burden on patients and caregivers or potential downsides of transfusions. The panel felt that the most important considerations were complications that may lead to hospitalization and burden but that the effects of transfusions on these were likely to be small.

The panel specifically pointed out 2 issues that should be considered when transfusion are advised for older adults with AML who are no longer receiving antileukemic therapy, following an established framework for risk consideration for transfusions. First, to initiate or continue these, patients need to show some benefit in terms of well-being. Second, patients need to understand, especially when they are in hospice, that such transfusions come with a “package” of potential downsides. This includes need to travel to clinics, potential transfusion reactions, and well-meaning but anxietyprovoking potential reassessments of goals of care by transfusion providers. Indeed, days spent in the outpatient clinic has been successfully used as a proxy for poor quality of life for older adults with AML.[125]

[…]

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.

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Alberta Health Services, 2019 [1].

Acute Myeloid Leukemia CLINICAL PRACTICE GUIDELINE LYHE-006

Zielsetzung/Fragestellung

To identify the management options for acute myeloid leukemias in adults including chemotherapy, hematopoietic stem cell transplantation, and palliation

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund fehlender höherwertiger Leitlinien (für jüngere Erwachsene) wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Pubmed and Medlinedatabases, ASCO abstracts and proceedings, and ASH abstracts and proceedings databases
- 2019 updates: Pubmed and Medline [..] ASH, ASCO and EHA abstracts and proceedings

LoE / GoR

Table 5. Levels of Evidence

Level	Description of Evidence
I	• evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias • meta-analyses of RCTs without heterogeneity
II	• small RCTs • phase II RCTs • large RCTs with potential bias or meta-analyses including such trials RCTs with heterogeneity
III	• prospective cohort studies • post-hoc and ad-hoc analyses of RCTs
IV	• retrospective cohort studies • case-control studies • instrument validation studies (*note:* could be level III, based on size of population, methods)
V	• studies without a control group • case reports • expert opinions • review articles or narrative reviews • Delphi studies • cross-sectional studies (interviews, focus groups, surveys)

Table 6. Strength of Recommendations

Grade	Description of Recommendation Strength
A	Strongly recommended; strong evidence for efficacy with a substantial clinical benefit.
B	Generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit.
C	Optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages.
D	Generally not recommended; moderate evidence against efficacy or for adverse outcomes.
E	Never recommended; strong evidence against efficacy or for adverse outcomes.

Empfehlungen zur Behandlung

SUMMARY OF RECOMMENDATIONS

1) All patients being considered for therapy should undergo a bone marrow aspiration and biopsy as well as peripheral blood films to establish a diagnosis and prognosis.
   a. Immunophenotyping by flow cytometry should be performed for diagnosis and to determine a leukemia-associated immunophenotype (LAIP) if possible.
   b. Samples should also be sent for cytogenetics, including fluorescence in-situ hybridization (FISH) where appropriate.
   c. Molecular analysis should be sent.
2) Ancillary Tests:
   a. Organ function should be assessed including liver, kidneys, coagulation and cardiac function.
   b. Blood group and human leukocyte antigen (HLA) typing of patient and family should be done as soon as possible in transplant eligible patients.
3) A lumbar puncture, with the installation of intrathecal chemotherapy, should be performed if worrisome unexplained neurological symptoms are present without a mass lesion by imaging.
   a. Consider a screening lumbar puncture in cases of myelomonocytic or monocytic acute myeloid leukemia (AML) or in those with a presenting white cell count of >40 x 10^9/L.
4) AML classification and risk stratification and transplant eligibility should be ascertained for all patients using age, performance status, World Health Organization (WHO) classification, cytogenetic and molecular risk group, as well response to therapy including minimal residual disease when possible. In the appropriate situations, establishing whether a genetic change is germline should be pursued.
5) Supportive care:
   a. In patients undergoing intensive chemotherapy a central venous catheter ideally should be placed.
   b. Red blood cell transfusions for symptomatic anemia.
   c. Platelets should be transfused at a threshold of 10 x 10^9/L if there is no evidence of bleeding or to keep a platelet level of around 50 x 10^9/L if there is active bleeding.
   d. Tumor lysis prophylaxis should be initiated in all patients.
   e. Antifungal prophylaxis should be considered during all phases of chemotherapy.
   f. Therapy of febrile neutropenia should include empiric broad spectrum antibiotics according to IDSA guideline.
   g. The use of growth factor support should be individualized.
   h. Steroid eye drops are recommended during the administration of intermediate to high dose cytarabine. These patients should also be screened for cerebellar toxicities before each dose of cytarabine.
   i. Sperm preservation should be discussed with male patients and a serum pregnancy test should be performed in female patients.
6) In transplant eligible patients treatment consists of induction and consolidation chemotherapy along with a FLT3 inhibitor in FLT3 positive cases
   a. Induction chemotherapy should consist of standard-dose cytarabine with an anthracycline
   b. Consolidation can consist of further cycles of chemotherapy alone or in association with a hematopoietic stem cell transplant depending on risk of relapse.
      i. Good risk – chemotherapy alone.
      ii. Intermediate risk – consider transplantation.
      iii. High risk – transplantation.
7) In transplant ineligible patients treatment options consist of palliation, low dose cytarabine, azacitidine or induction chemotherapy, depending on performance status and risk stratification. Strong consideration should be given to enrollment into a clinical trial.
8) In the instance of relapse re-induction chemotherapy can be considered depending on performance status, otherwise palliation should be instituted.

Hintergrundinfomation

Transplant Eligible Patients

Table 8. Prognosis by European LeukemiaNet Risk group in Younger patients (<60 years of age)[102]

Risk	N	CR (%)	DFS (%)	OS (%)	Median DFS (years)	Median OS (years)
Favourable*	339	95	55	66	5.5	11.5
Intermediate I**	144	76	23	28	0.8	1.2
Intermediate II***	156	79	34	45	1.2	2.1
Adverse****	179	50	10	12	0.6	0.8

N=number of patients, CR=complete remission, DFS= disease free survival, OS=overall survival
* t(8;21)(q22;q22); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11, Mutated NPM1 without FLT3-ITD (normal karyotype), Mutated CEBPA (normal karyotype)
**Mutated NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 without FLT3-ITD (normal karyotype)
***t(9;11)(p22;q23); MLLT3-MLL, Cytogenetic abnormalities not classified as favorable or adverse
****inv(3)/(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, t(6;9)(p23;q34); DEK-NUP214, t(v;11)(v;q23); MLL rearranged, -5 or del(5q), -7, abnl(17p), Complex karyotype (three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions).

Induction

Chemotherapy should consist of standard-dose cytarabine with an anthracycline, so called 7&3 chemotherapy (see appendix A for regimens). Studies looking at higher doses of cytarabine in induction have not shown an increased CR rate but have demonstrated an increased treatment related mortality[103-105]. At count recovery or about day 28-35 from the start of chemotherapy a bone marrow aspirate should be done to determine remission status. The likelihood of establishing a CR with one cycle of induction chemotherapy varies amongst prognostic groups but overall is in the order of 60-70%. Consider repeating cytogenetic analysis if initially abnormal as part of the remission documentation[29].Other regimens such as FLAG (fludarabine + high-dose cytarabine + G-CSF) or NOVE (mitoxantrone + etoposide) may need to be considered in the case of significant left ventricular dysfunction.

Re-induction

If CR is not achieved after one cycle of induction chemotherapy another attempt is appropriate. This may consistent of a repeat of 7&3 chemotherapy or alternatively a different regimen such as NOVE, NOVE-HiDAC80, FLAG-Ida (FLAG + idarubicin), or high dose cytarabine (HiDAC) (see appendix A for regimens) may be tried. A bone marrow aspirate and biopsy should be done at count recovery or day 30-35 to document remission status. The likelihood of a second regimen being successful is in the order of 50%. If no remission is achieved after 2 cycles of induction chemotherapy palliation may become the goal of care.

Consolidation

If CR has been achieved further therapy is necessary for potential cure. The nature of consolidation therapy must be individualized for each patient based on a risk analysis of the risk of relapse of the AML versus the risk of the proposed consolidation therapy. This will depend on prognostic features of the leukemia, response to therapy, performance status and type of hematopoietic stem cell donor available. **HiDAC is the mainstay of consolidation chemotherapy** as there has been shown to be a dose intensity effect to cytarabine suggesting that HiDAC is beneficial in induction or consolidation[103,104]. Generally at least one cycle is administered in all patients if only to allow for planning of an allogeneic stem cell transplant although the absolute need for this is controversial.

Good risk patients: In patients with AML with t(8;21) or inv 16, data suggests that provided there are no additional risk factors multiple cycles of HiDAC provide higher overall survival than lower doses of cytarabine or stem cell transplant[106-109].Our recommendation is 3-4 cycles of HiDAC post induction chemotherapy. A recent retrospective study from Edmonton and Vancouver found similar outcomes with 2 cycles of consolidation compared with 3[110], but this requires confirmation in a prospective study. There is also evidence that the addition of gemtuzumab ozogamicin (GO) may produce better outcomes when combined with chemotherapy[111]; however, this agent is not yet approved in Canada.

Intermediate risk patients: HiDAC has been shown to be preferable over lower dose cytarabine in this cytogenetic group as well[26,107] but its superiority over stem cell transplantation has not been established. It is generally recognized that an allogeneic stem cell transplant provides a decreased relapse rate at a

cost of increased treatment related mortality when compared to consolidation chemotherapy or autologous transplantation[109,112-114]. The transplant related mortality gap between matched related and unrelated donors has been shown to be significantly reduced in recent years[115,116]. A suitable hematopoietic stem cell donor should be sought. If a matched sibling donor is found a related myeloablative stem cell transplant should proceed as soon as possible, ideally after one dose of HiDAC. If there are no suitable family donors, the patient should proceed through 3-4 cycles of HiDAC consolidation while a match unrelated donor is sought. If one is found before the third cycle of consolidation chemotherapy, consider matched unrelated donor stem cell transplantation.

High risk patients: All efforts should be undertaken to find a matched donor, related or unrelated for eligible patients. During that time the patient should receive ongoing cycles of HiDAC chemotherapy up to a total of 4 cycles. The patient should proceed to allogeneic stem cell transplantation as soon as a donor is identified. If no fully matched donor is available consideration should be given to a haploidentical related transplant if a suitable donor is available. Finally, unrelated cord blood transplantation is also an option in selected situations.

FLT3 Mutation Positive Patients

If not enrolled on a clinical trial with a FLT3 inhibitor, **midostaurin should be added for these patients on day 8 of each induction and consolidation treatment cycle, as per the RATIFY clinical trial protocol (midostaurin and standard induction/consolidation chemotherapy).** The Phase III RATIFY (CALGB 10603) trial randomized 717 AML patients with FLT3 mutation to receive standard induction and consolidation chemotherapy +/- midostaurin. After a median follow-up of 57 months, patients in the midostaurin arm had a significant improvement in median overall survival vs. placebo (74.7 months vs. 26 months, respectively; p=0.007), representing a 23% reduction in the risk for death[49]. It has now been approved by Health Canada for this indication.

Transplant Ineligible Patients

Table 9. Prognosis by European LeukemiaNet Risk factor in Elderly patients (≥60 years of age)[102]

Risk	N	CR (%)	DFS (%)	OS (%)	Median DFS (years)	Median OS (years)
Favourable*	145	83	24	33	1.1	1.6
Intermediate I**	136	61	10	11	0.6	0.9
Intermediate II***	229	63	11	16	0.7	0.9
Adverse ******	229	39	6	3	0.5	0.5

N=number of patients, CR=complete remission, DFS= disease free survival, OS=overall survival
* t(8;21)(q22;q22); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11, Mutated NPM1 without FLT3-ITD (normal karyotype), Mutated CEBPA (normal karyotype)
**Mutated NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 and FLT3-ITD (normal karyotype), Wild-type NPM1 without FLT3-ITD (normal karyotype)
***t(9;11)(p22;q23); MLLT3-MLL, Cytogenetic abnormalities not classified as favorable or adverse
****inv(3)/(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1, t(6;9)(p23;q34); DEK-NUP214, t(v;11)(v;q23); MLL rearranged, -5 or del(5q), -7, abnl(17p), Complex karyotype (three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions).

In patients with a normal karyotype, the remission rate on older patients is 50-60% with cytarabine combined with idarubicin, daunorubicin or mitoxantrone. In those with adverse risk cytogenetics the chance of achieving a remission is approximately 25%, with median OS of approximately 6 months[25,26,123]. Attempts to modify this by adjusting the chemotherapy regimens, adding growth factors or multidrug resistance protein regulators have not been successful[17,124-126]. Due to the poor outcomes in this group, **clinical trials are particularly important. However, if none are available, azacitidine would be appropriate therapy in older patients with high-risk cytogenetics who are not considered candidates for allogeneic HSCT. In other elderly non-fit patients, low-dose cytarabine would also be appropriate.**

Induction

In patients with an ECOG performance status of 2 or less and no prohibitive comorbid conditions, standard 7&3 induction chemotherapy is appropriate[127], particularly in patients with core-binding factor leukemias. If consideration is being given to consolidation therapy or re-induction in the case of primary induction failure, a bone marrow aspirate should be performed to document remission. If no further therapy is planned this can be omitted.

Consolidation

Consolidation chemotherapy in this group of patients is controversial. There is evidence to suggest that low-dose, prolonged ambulatory treatment should be preferred to intensive chemotherapy[123]; however intermediate dose cytarabine can be considered if the patient maintains a good performance status, normal renal function, and has a good or normal karyotype. Consolidation has not been shown to prolong survival in patients with high risk karyotypes. There is limited retrospective data which suggests azacitidine may be appropriate in this setting, although prior cytotoxic therapy was associated with a decreased marrow response rate, azacitidine treatment still prolonged overall survival[128]. LDAC may also be considered in patients in CR who are not suitable candidates for further intensive chemotherapy.

New Therapies

Gemtuzumab ozogamicin (GO)

the anti-CD33 antibody carrying a toxic calicheamicin-γ1 derivative, which after intracellular hydrolytic release, induces DNA strand breaks, apoptosis, and cell death was the first anti-cancer immunoconjugate to obtain regulatory approval in the United States. It was subsequently withdrawn from the US by Pfizer after results from the S0106 trial demonstrated no overall survival benefit, while reporting an increased rate of early mortality in the GO arm of patients 18-60 years old with de novo AML receiving 2 cycles of induction chemotherapy with daunorubicin/cytarabine with or without GO (6 mg/m2)105. However, emerging data from other well controlled studies did report benefits from the addition of GO to chemotherapy, particularly when used in smaller fractionated doses[138-141]. **A recent metanalysis of 5 randomized trials found an overall survival benefit for GO when added to intensive chemotherapy, most strikingly seen in patients with favourable risk cytogenetics, while those with adverse risk karyotypes did not benefit**[111]. In September 2017 GO was approved by the FDA for this indication. It is currently under review by Health Canada (February 2019) and available via compassionate access.

[..]

Another promising agent is **venetoclax**, a selective oral small molecule BCL-2 inhibitor. Although it has limited activity as a single agent, it has been found to synergize with chemotherapy agents in preclinical models. In a study by Wei et al, venetoclax 600 mg daily was given in combination with low dose cytarabine to patients with newly diagnosed AML not eligible to receive intensive induction chemotherapy[148]. Of the 82 patients evaluable, 44 (54%) achieved CR or CR with incomplete count recovery (CRi), demonstrating that this is an active combination in patients with newly diagnosed AML. Venetoclax in combination with azacitdiine or decitabine was evaluated in older patients with AML unfit to receive intensive chemotherapy. Of the 145 patients enrolled, 67%of patients achieved CR/CRi. The median duration of response was 11.3 months[149].

These regimens are now under evaluation in Phase III randomized clinical trials. Phase I studies are also ongoing adding it to intensive remission inducing chemotherapy. It has been approved by the FDA in patients over the age of 75 with de novo AML in combination with low dose cytarabine or hypomethylating agents as of November 2018.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2023) am 23.10.2023

#	Suchfrage
1	[mh "leukemia, myeloid, acute"]
2	(acute AND leu*mia*):ti,ab,kw
3	(myeloid* OR myelogen* OR myeloblast* OR myelocyt*):ti,ab,kw
4	AML:ti,ab,kw
5	#1 OR (#2 AND #3) OR #4
6	#5 with Cochrane Library publication date from Oct 2018 to present

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#	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 (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR

#	Suchfrage
	proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
8	((#7) AND ("2018/10/01"[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] OR preprint[pt])

Leitlinien in PubMed am 23.10.2023

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 ("2018/10/01"[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] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 23.10.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- 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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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-302-z

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) Bundesärztekammer, Dezernat 1 – Ärztliche Versorgung und Arzneimittel, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	2. November 2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Erwachsene mit neu diagnostizierter akuter myeloischer Leukämie (AML), die eine Mutation von FLT3 (FMS-like tyrosine kinase 3) aufweisen.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Der gegenwärtige Behandlungsstandard stellt sich wie folgt dar (1): **I) Patienten „fit“**, d. h. < 60–75 Jahre alt, ohne schwere Komorbidität **a) Induktion:** Die Standardtherapie für jüngere Patienten in ausreichendem Allgemeinzustand besteht aus einer konventionellen Induktionschemotherapie (überwiegend verwendet „3 + 7“, das heißt Daunorubicin über drei Tage und Cytarabin über sieben Tage), gefolgt von Midostaurin, letzteres Arzneimittel gegeben ab Ende der Chemotherapie für zwei Wochen, das heißt in der Regel Tag 8–21 eines Therapiezyklus. Je nach Ansprechen und Zustand des Patienten erfolgt eine 2. gleichartige Induktion, eine modifizierte 2. Induktion (meist unter Einschluss von hoch dosiertem Cytarabin) oder Verzicht auf eine 2. Induktion. Im Anschluss daran existieren mehrere mögliche Therapieoptionen b) und c): **b1) Allogene Stammzelltransplantation:** Entweder in Remission aufgrund eines bereits primär erhöhten Rezidivrisikos oder bei unzureichendem Ansprechen. Die allogene Transplantation bietet die größte Chance auf eine langfristige Remission, ist jedoch auch mit erheblichen Risiken für therapiebedingte Morbidität und Mortalität verbunden. Die Indikation zur allogenen Transplantation in 1. Remission ist eine Kann-Entscheidung, wenn keine zusätzlichen Risikofaktoren vorliegen. Der früheste übliche Zeitpunkt für die Stammzelltransplantationen ist nach einem Zyklus Induktionschemotherapie. Häufig wird auch nach zwei Zyklen Induktionschemotherapie oder Induktion plus einem Zyklus Konsolidierung (siehe c1)

transplantiert. Bei unzureichendem Ansprechen ist eine Transplantation auch später im Verlauf indiziert, wenn der Zustand der Patienten dies zulässt.

b2) Erhaltungstherapie nach Transplantation:
Im Anschluss an eine allogene Stammzelltransplantation ist eine Erhaltungstherapie mit einem gegen FLT3 wirksamen Tyrosinkinase-Inhibitor zu diskutieren. Daten aus randomisierten Studien liegen hierfür für Sorafenib vor, das allerdings für diese Indikation nicht zugelassen ist (2, 3). Zudem stammen diese Daten aus einer Zeit, in der Midostaurin noch keinen Standard in der Induktionstherapie darstellte. Trotzdem wird Sorafenib in der aktuellen Onkopedia-Leitlinie empfohlen (1). Midostaurin wurde ebenfalls für die Erhaltungstherapie nach allogener Stammzelltransplantation eingesetzt und dabei die Machbarkeit und Verträglichkeit dieser Strategie belegt, jedoch im Rahmen eines Gesamtkonzeptes, das den spezifischen Zusatznutzen der Midostaurin-Erhaltungstherapie nicht sicher definieren kann (4). Es besteht keine spezifische Zulassung für Midostaurin als Erhaltungstherapie nach allogener Transplantation.

c1) Chemotherapie-Konsolidierung:
Fortführung der Therapie mit konsolidierender Chemotherapie (in der Regel hochdosiertes oder mittelhochdosiertes Cytarabin), jeweils gefolgt von Midostaurin an Tag 8–21 des Zyklus. Dies ist indiziert, wenn die Entscheidung unter Abwägung von Therapieerfolg, Chancen und Risiken gegen eine allogene Transplantation gefallen ist oder zur Überbrückung, wenn die Transplantation nicht kurzfristig durchgeführt werden kann.

c2) Erhaltungstherapie nach Induktion und Konsolidierung:
Eine Erhaltungstherapie kommt infrage für Patienten, bei denen keine allogene Transplantation geplant ist. Es existieren zwei Optionen, beide sind in Deutschland zugelassen:

- Erhaltungstherapie mit Midostaurin: In der Zulassungsstudie wurde Midostaurin in einem Paket als Teil von Induktion, Konsolidierung und in der Erhaltungstherapie geprüft. Der Zusatznutzen von Midostaurin spezifisch in der Erhaltungstherapie ist unklar und nach vorliegenden Publikationen eher kritisch zu sehen (5).
- Erhaltungstherapie mit oralem Azacitidin: Diese Erhaltungstherapie führte in einer randomisierten Studie zu einem verlängerten Überleben für Patienten in Remission, für die unter Abwägung von Chancen und Risiken eine allogene Transplantation als nicht indiziert erachtet wurde. Dieser Unterschied besteht auch für die Subgruppe der Patienten, deren AML eine FLT3-Mutation aufwies (6, 7).

II) Patienten nicht ausreichend „fit“ für eine Induktionschemotherapie
Patienten mit AML, denen aufgrund von Alter, Allgemeinzustand oder Nebendiagnosen keine Induktionstherapie angeboten werden kann, wird in der Regel eine palliativ intendierte Therapie angeboten, heute bevorzugt mit Azacitidin (oder Decitabin) plus Venetoclax. Mit einer solchen Kombinationstherapie können ebenfalls komplette Remissionen erreicht werden. Spezifische Therapieansätze bei Nachweis einer FLT3-ITD-Mutation sind für diese Patientengruppe bisher nicht etabliert.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Entscheidungskriterien sind bereits oben bei den Therapieoptionen mit aufgeführt. Hier nochmals kurz zusammengefasst:

Patient fit für Induktion?
Für eine Induktion sprechen: jüngeres biologisches Alter, gute Leistungsfähigkeit nach WHO/ECOG, Fehlen von schweren Begleiterkrankungen, Patientenwunsch nach entsprechender Aufklärung.

Allogene Transplantation?
Für eine Transplantation sprechen: zusätzliche ungünstige genetische Risikofaktoren, unzureichendes Ansprechen nach Induktion (fehlende Remission oder eindeutig nachweisbare Resterkrankung), unkomplizierter Therapieverlauf unter Induktion, jüngeres Alter, gute Leistungsfähigkeit nach WHO/ECOG, Fehlen von schweren Begleiterkrankungen, Patientenwunsch nach entsprechender Aufklärung. Sonderfall: Eine allogene Transplantation kann auch bei ursprünglich nicht als fit eingeschätzten Patienten erwogen werden, wenn unter Azacitidin plus Venetoclax eine Remission bei gleichzeitiger Besserung des Allgemeinzustandes erreicht wird.

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