Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-171 Mepolizumab

Stand: November 2021

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

Mepolizumab
[zur Behandlung des hypereosinophilen Syndroms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet**
Zu bewertendes Arzneimittel:	
Mepolizumab	Geplantes Anwendungsgebiet laut Beratungsanforderung: Behandlung des hypereosinophilen Syndroms
Imatinib L01XE01 Glivec®	Erwachsene mit fortgeschrittenem hypereosinophilem Syndrom (HES) und/oder chronischer eosinophiler Leukämie (CEL) mit FIP1L1-PDGFRα-Umlagerung (Stand Fachinfo: Mai 2019)

Quellen: AMIS-Datenbank, Fachinformation

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-171 (Mepolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Dezember 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Hypereosinophiles Syndrom (HES) ohne erkennbare nicht-hämatologische Sekundärursache

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

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 27.09.2021 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 245 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 wurde insgesamt drei Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenz.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Leitlinien

Butt NM et al., 2017 [1].

British Committee for Standards in Haematology (BCSH)

Guideline for the investigation and management of eosinophilia

Zielsetzung/Fragestellung

The purpose of this guideline is to provide a practical approach to the investigation and management of eosinophilia.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: keine Betroffenen beteiligt.
- Interessenkonflikte angegeben, finanzielle Unabhängigkeit unklar.
- Systematische Suche; Auswahl und Bewertung der Evidenz unklar (siehe sonstige methodische Hinweise).
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität ist unklar

Recherche/Suchzeitraum:

- PubMed and EMBASE until August 2015

LoE/GoR

Table I. Evidence statements and grades of recommendations.

GRADE nomenclature
Strength of recommendations
Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'
Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'
Quality of evidence
The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty
(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations
(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision wide confidence intervals or methodological flaws e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient)
(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion

Sonstige methodische Hinweise

- Laut Publikation basiert die Einschätzung der „quality of evidence“ auf einer Bewertung mittels GRADE. In diese Einschätzung fließt regelhaft eine Einschätzung des Biasrisikos ein. Ergebnisse der Biasrisikobewertung sind der Publikation nicht zu entnehmen.

Empfehlungen

Treatment of patients with eosinophilia

The treatment of eosinophilia should be directed at the underlying cause. Specific treatment of secondary (reactive) eosinophilia is outside of the scope of this guideline and specialist referral should be made where indicated. Some patients with chronic marked eosinophilia may never experience end-organ damage and treatment of eosinophilia in this circumstance is not merited. Emergency treatment, treatment of clonal eosinophilia and treatment of idiopathic HES are dealt with below and summarised in Fig 2.

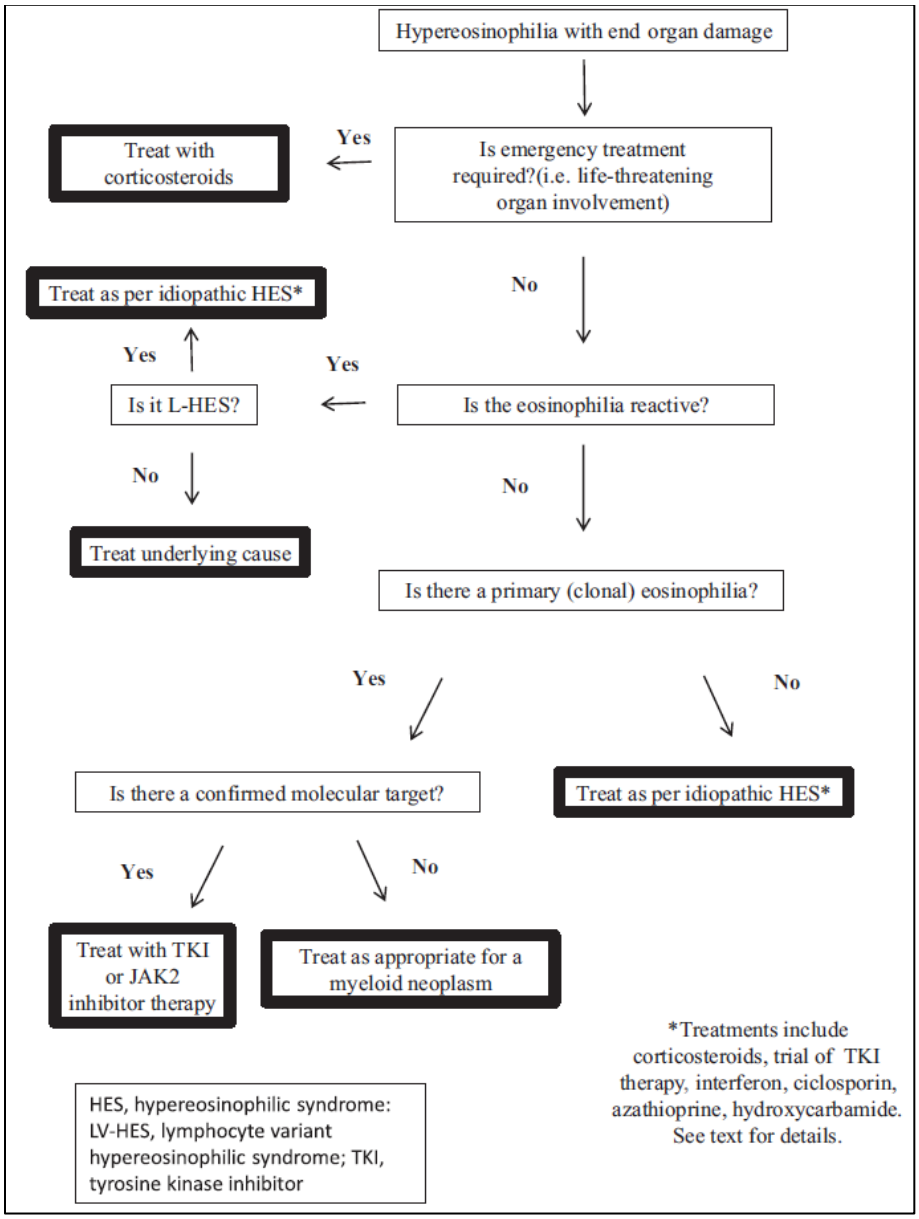

Fig 2. Algorithm for the treatment of eosinophilia.

Emergency treatment

- Patients requiring emergency treatment for severe or life-threatening eosinophilia should receive high-dose corticosteroids (**Grade 1B**).
- Patients receiving corticosteroids, in whom there is a risk of strongyloides infection, should receive concomitant ivermectin to prevent potentially fatal hyperinfection (**Grade 1B**)

There is no consensus on the absolute eosinophil level in the peripheral blood at which treatment is deemed necessary in completely asymptomatic patients (Gotlib, 2014). The absolute eosinophil count does not correlate well with the degree or risk of organ damage (Flaum et al, 1981; Schooley et al, 1981; Brito-Babapulle, 2003). There is some evidence for urgent treatment in cases with a high count of degranulated eosinophils because cardiac damage has been found to correlate with a degranulated eosinophil count of 1x109/l or more (Spry et al, 1983). In the absence of identified organ damage, there is no evidence to indicate when or if treatment should be initiated. However in cases with significant organ dysfunction, particularly cardiac or pulmonary, emergency treatment is required. The aim of therapy is to reduce the absolute eosinophil count and reduce tissue infiltration and eosinophil-mediated tissue

damage (Klion, 2009). A response assessment has been proposed by the Nordic study group based on (i) normalisation of eosinophil count, other haematological parameters and biochemical indicators, such as IgE and serum tryptase; (ii) no evidence of organ involvement or symptoms; (iii) quality of life assessment (Bjerrum et al, 2012). This has yet to be validated.

Corticosteroids: High dose corticosteroids are the mainstay of emergency treatment and may be indicated whilst awaiting the results of initial investigations. The evidence for their use is limited and largely restricted to numerous case reports and small case series, many of which were published prior to the understanding of the molecular characterisation of hypereosinophilic syndromes (Weller & Bubley, 1994; Klion et al, 2006; Roufosse & Weller, 2010; Simon & Klion, 2012). Although there is no evidence for the use of corticosteroids in combination with other immunosuppressive or myelosuppressive agents as first line therapy, this may be prudent to lessen eosinophil-mediated tissue damage. Where there is evidence of life-threatening organ involvement treatment should start with the equivalent of 1 mg/ kg/day of methylprednisolone intravenously. Otherwise, oral prednisolone is generally used at a dose of 0.5–1 mg/kg/day for 1 – 2 weeks. In extreme eosinophilia, consideration could be given to the concomitant administration of allopurinol for a short period. Corticosteroids can be slowly tapered over a period of 2 – 3 months to the lowest possible maintenance dose to retain response. Complete and partial response rates vary, typically between 64% and 85% (Ogbogu et al, 2009; Helbig et al, 2013, 2014) with reported maintenance doses of prednisone (or equivalent) ranging widely between 1 and 60 mg daily for periods between 2 months and 20 years. The toxicity of long-term corticosteroids needs to be considered, and measures should be taken to limit the risk. In patients with a strong possibility of strongyloides exposure (see Table III), concomitant empirical ivermectin therapy should be given (200 µg/kg/ day for 2 days) to prevent potentially fatal hyperinfection (Ramanathan & Nutman, 2008). Steroid-unresponsive cases may require alternative therapeutic approaches and it has been proposed that in cases where the eosinophil count remains greater than 1,5 x 10^9/l after 1 month of therapy or if a patient requires a maintenance dose of prednisolone (or equivalent) of greater than 10 mg daily, a second-line agent should be considered (see Treatment of idiopathic hypereosinophilic syndrome).

Referenzen:

Weller, P.F. & Bubley, G.J. (1994) The idiopathic hypereosinophilic syndrome. Blood, 83, 2759–2779.
Klion, A.D., Bochner, B.S., Gleich, G.J., Nutman, T.B., Rothenberg, M.E., Simon, H.U., Wechsler, M.E. & Weller, P.F.; The Hypereosinophilic Syndromes Working Group. (2006) Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. The Journal of Allergy and Clinical Immunology, 117, 1292–1302.
Roufosse, F. & Weller, P.F. (2010) Practical approach to the patient with hypereosinophilia. The Journal of Allergy and Clinical Immunology, 126, 39–44.
Simon, H.U. & Klion, A. (2012) Therapeutic approaches to patients with hypereosinophilic syndromes. Seminars in Hematology, 49, 160–170.
Ogbogu, P.U., Bochner, B.S., Butterfield, J.H., Gleich, G.J., Huss-Marp, J., Kahn, J.E., Leiferman, K.M., Nutman, T.B., Pfab, F., Ring, J., Rothenberg, M.E., Roufosse, F., Sajous, M.H., Sheikh, J., Simon, D., Simon, H.U., Stein, M.L., Wardlaw, A., Weller, P.F. & Klion, A.D. (2009) Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. The Journal of Allergy and Clinical Immunology, 124, e1313.
Helbig, G., Wisniewska-Piaty, K., Francuz, T., Dziaczkowska-Suszek, J. & Kyrcz-Krzemien, S. (2013) Diversity of clinical manifestations and, response to corticosteroids for idiopathic hypereosinophilic syndrome: retrospective study in 33 patients. Leukaemia & Lymphoma, 54, 807–811.
Helbig, G., Hus, M., Francuz, T., Dziaczkowska-Suszek, J., Soja, A. & Kyrcz-Krzemien, S. (2014) Characteristics and clinical outcome of patients with hypereosinophilia of undetermined significance. Medical Oncology, 31, 815.
Ramanathan, R. & Nutman, T. (2008) Strongyloides stercoralis infection in the immunocompromised host. Current Infectious Disease Reports, 10, 105–110.

Treatment of clonal eosinophilia

- Patients with clonal eosinophilia with FIP1L1-PDGFRA (including patients presenting with acute leukaemia), should be treated with low dose imatinib (**Grade 1B**)
- Patients with clonal eosinophilia with PDGFRB rearrangement or ETV6-ABL1 fusion should receive standard dose imatinib (**Grade 1B**)

- Patients with clonal eosinophilia with ETV6-FLT3 fusion should be considered for sunitinib or sorafenib therapy (**Grade 2B**)
- Patients with clonal eosinophilia with JAK2 rearrangement should be considered for ruxolitinib therapy (**Grade 2B**)
- Patients with acute myeloid leukaemia with clonal eosinophilia and no molecular or cytogenetic abnormality suggesting likely response to a tyrosine kinase inhibitor should be offered standard AML induction therapy (**Grade 1A**)
- Patients with other haematological neoplasms with clonal eosinophilia should have treatment directed at management of the neoplasm. If there is organ damage or dysfunction relating to the eosinophilia, treatment with corticosteroids should also be given (**Grade 1C**)

Chronic leukaemias with clonal eosinophilia and a specific molecular target. In clonal eosinophilia the highest priorities are to provide emergency treatment when required and to recognise entities in which specific therapy with a tyrosine kinase inhibitor (TKI) is indicated […]. Patients with significant organ dysfunction, particularly cardiac or pulmonary, require emergency corticosteroid treatment alongside specific TKI therapy when appropriate.
Cases associated with FIP1L1-PDGFRA are highly sensitive to imatinib and a starting dose of 100 mg daily should be commenced (Baccarani et al, 2007). Dose titration, up to 400 mg daily, is dependent on eosinophil count and molecular response. Imatinib should also be commenced in patients presenting in acute leukaemic transformation as they may enter remission with imatinib even in the absence of chemotherapy (Barraco et al, 2014). Acquired imatinib resistance is uncommon but a T674I mutation, and less commonly a D842V mutation, leading to multi-TKI resistance has been observed in some cases.
Cases associated with PDGFRB rearrangement or an ETV6-ABL1 fusion gene are responsive to imatinib at a dose of 400 mg daily. Molecular monitoring is indicated. Neoplasms associated with ETV6-FLT3 may be responsive to sunitinib or sorafenib (Walz et al, 2011).
Ruxolitinib has demonstrated activity in cases with PCM1-JAK2 or other JAK2 rearrangement. Doses are adapted to platelet counts in line with the summary of product characteristics for ruxolitinib. Although a complete remission may be achieved, this is often of limited duration (Schwaab et al, 2015b).
Chronic leukaemias with clonal eosinophilia without a specific molecular target. Clonal disorders without a specific molecular targeted therapy can be treated as for idiopathic HES as described below. Some patients may respond to imatinib though they often require higher doses of this agent and seem to respond more slowly (Metzgeroth et al, 2008; Butterfield, 2009). In view of the good safety profile of this agent, a short trial of imatinib 400 mg daily for 4 - 6 weeks is justified. Patients with at least four features of an MPN are more likely to respond to imatinib (Khoury et al, 2016).
Cases associated with FGFR1 rearrangement have a poor prognosis and intensive AML-type induction treatment followed by HSCT may be the best option. Because of the poor prognosis of CEL, NOS (Helbig et al, 2012) this approach could also be justified in these cases. Response is assessed by monitoring a clonal marker when possible and by the eosinophil count.
Other haematological malignancies with an associated clonal eosinophilia. Patients with AML with clonal eosinophilia and no identifiable molecular or cytogenetic abnormality should be offered standard AML induction therapy. In patients with other haematological neoplasms with an associated clonal eosinophilia, treatment should be directed towards management of the underlying cause. If there is organ damage or dysfunction relating to the eosinophilia, addition of corticosteroids is indicated.

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Barraco, D., Carobolante, F., Candoni, A., Simeone, E., Piccaluga, P., Tabanelli, V. & Fanin, R. (2014) Complete and long-lasting cytologic and molecular remission of FIP1L1-PDGFRA positive acute eosinophil myeloid leukaemia, treated with low-dose imatinib monotherapy. European Journal of Haematology, 92, 541–545.
Butterfield, J.H. (2009) Success of short-term, higher-dose imatinib mesylate to induce clinical response in FIP1L1-PDGFRalpha-negative hypereosinophilic syndrome. Leukemia Research, 33, 1127–1129.

Helbig, G., Soja, A., Bartkowska-Chrobok, A. & Kyrcz-Krzemien, S. (2012) Chronic eosinophilic leukemia-not otherwise specified has a poor prognosis with unresponsiveness to conventional treatment and high risk of acute transformation. American Journal of Hematology, 87, 643–645.
Khoury, P., Desmond, R., Pabon, A., Holland-Thomas, N., Ware, J.M., Arthur, D.C., Kurlander, R., Fay, M.P., Maric, I. & Klion, A.D. (2016) Clinical features predict responsiveness to imatinib in platelet derived growth factor receptor alpha-negative hypereosinophilic syndrome. Allergy, 71, 803–810.
Metzgeroth, G., Walz, C., Erben, P., Popp, H., Schmitt-Graeff, A., Haferlach, C., Fabarius, A., Schnittger, S., Grimwade, D., Cross, N.C., Hehlmann, R., Hochhaus, A. & Reiter, A. (2008) Safety and efficacy of imatinib in chronic eosinophilic leukaemia and hypereosinophilic syndrome: a phase-II study. British Journal of Haematology, 143, 707–715.
Schwaab, J., Knut, M., Haferlach, C., Metzgeroth, G., Horny, H.P., Chase, A., Tapper, W., Score, J., Waghorn, K., Naumann, N., Jawhar, M., Fabarius, A., Hofmann, W.K., Cross, N.C. & Reiter, A. (2015b) Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. Annals of Hematology, 94, 233–238.
Walz, C., Erben, P., Ritter, M., Bloor, A., Metzgeroth, G., Telford, N., Haferlach, C., Haferlach, T., Gesk, S., Score, J., Hofmann, W.K., Hochhaus, A., Cross, N.C. & Reiter, A. (2011) Response of ETV6-FLT3-positive myeloid/lymphoid neoplasm with eosinophilia to inhibitors of FMS-like tyrosine kinase 3. Blood, 118, 2239–2242.

Treatment of lymphocytic variant of hypereosinophilic syndrome

- Patients with the lymphocytic variant of hypereosinophilic syndrome (HES) can be managed in the same manner as idiopathic HES (**Grade 2B**)

  Appropriate management is similar to that of idiopathic HES (see under relevant heading). Corticosteroids are indicated for primary management. Ciclosporin may be useful as a steroid-sparing agent and mepolizumab has shown efficacy in this setting (Rothenberg et al, 2008; Ogbogu et al, 2009).

Referenzen:
Rothenberg, M.E., Klion, A.D., Roufosse, F.E., Kahn, J.E., Weller, P.F., Simon, H.U., Schwartz, L.B., Rosenwasser, L.J., Ring, J., Griffin, E.F., Haig, A.E., Frewer, P.I., Parkin, J.M. & Gleich, G.J. (2008) Treatment of patients with the hypereosinophilic syndrome with mepolizumab. New England Journal of Medicine, 358, 1215–1228.
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Treatment of idiopathic hypereosinophilic syndrome

- Patients with idiopathic HES should be treated in the first instance with corticosteroids (see emergency treatment above).

  Corticosteroids: In general, corticosteroids are the first-line therapy for idiopathic HES, and immunomodulatory and myelosuppressive agents are reserved for steroid-unresponsive disease or are used as adjuvant steroid-sparing therapy.

- Patients with idiopathic HES who do not respond adequately to corticosteroids, or who require prolonged corticosteroid therapy, or who are intolerant of corticosteroids, should be considered for a short trial (4 – 6 weeks) of imatinib, immunomodulatory agents (interferon alpha, ciclosporin or azathioprine), myelosuppressive therapy (hydroxycarbamide) or monoclonal antibody therapy with mepolizumab (anti-interleukin 5), the latter preferably as part of a clinical trial (**Grade 2B**).

  Imatinib: As in cases of clonal eosinophilia without a specific molecular target, patients with idiopathic HES failing first line corticosteroids should be considered for a short trial (4 – 6 weeks) of imatinib 400 mg daily given the good safety profile of this agent.

Immunomodulatory agents.
Interferon-alpha: Interferon-alpha targets both eosinophils and T cells, making it a rational therapy for many hypereosinophilic disorders. Its mechanism of action and role in the treatment of hypereosinophilic syndromes including idiopathic HES have been extensively reviewed (Butterfield, 2005). Improvement in the eosinophil count is associated with improvement in organ dysfunction including clinical symptoms and organomegaly (hepatomegaly, splenomegaly or both) (Murphy et al, 1990; Zielinski & Lawrence, 1990; Fruehauf et al, 1993), cardiopulmonary effects (Yamada et al, 1998), mucosal ulcers (Barouky et al, 2003) and cutaneous manifestations (Mohr et al, 1995). It may take several weeks to achieve a response. The optimal starting dose of interferon-alpha in hypereosinophilic disorders has yet to be defined. A wide variety of effective doses have been reported between 1 and 5 million units/m^2/day (Butterfield, 2005). The side effects are usually dose dependent and frequently dose limiting (Ogbogu et al, 2009). Maintenance doses may be lower than initiation doses (Busch et al, 1991; Canonica et al, 1995). There are limited data on the efficacy of once weekly pegylated-interferon as an alternative to conventional interferonalpha (Butterfield & Weiler, 2012).
Ciclosporin: ciclosporin is a calcineurin inhibitor that is used primarily in HES as a steroid-sparing immunosuppressive agent despite a relative paucity of published information, largely limited to case reports. Ciclosporin impairs T-cell activation hence its value in lymphocytic-variant HES. There are also reports of sustained clinical responses when ciclosporin is added to prednisolone in previously steroid-resistant idiopathic HES (Zabel & Schlaak, 1991; Akiyama et al, 1997; Fukuta et al, 2001) and when used as a steroid-sparing agent in idiopathic paediatric HES (Nadarajah et al, 1997; Hosoki et al, 2011) [and also in cases of eosinophilic cellulitis and fasciitis (Kim et al, 2013; Tahara et al, 2008)]. A variety of effective ciclosporin doses have been reported, generally with gradual tapering following clinical response. The largest published experience in HES is that of 11 patients (within a 188-patient retrospective case series) who received ciclosporin at doses of 150 to 500 mg/24 h (median 200 mg); of the 5 patients who received ciclosporin monotherapy, 1 patient achieved a complete response with 2 partial responders although, notably, ciclosporin was discontinued early in 9 of the 11 patients, due to either lack of efficacy or poor tolerance (Ogbogu et al, 2009).
Azathioprine: azathioprine is a purine analogue used commonly in combination with corticosteroids as a steroidsparing agent. There are case reports of its use in hypereosinophilic syndromes, particularly in those presenting with cardiological complications including endomyocardial fibrosis (Pineton de Chambrun et al, 2015) and eosinophilic myositis (Aggarwal et al, 2001; Fozing et al, 2014). The recommended starting dose is 1–3 mg/kg/day and this should be adjusted, within these limits, depending on the clinical and haematological response. This may not be evident for weeks or months. Lower starting doses should be considered in patients with renal and/or hepatic insufficiency or those receiving concomitant allopurinol.

Myelosuppressive therapy.
Hydroxycarbamide: hydroxycarbamide is a non-alkylating ribonucleotide reductase inhibitor, which has been used as a myelosuppressive agent at dose of 0.5–3 g daily to lower the eosinophil count as a corticosteroid-sparing agent either alone (Ogbogu et al, 2009) or in combination with interferon alpha (Butterfield, 2005). Other myelosuppressive therapy: haematological benefit has been observed with other agents, such as vincristine, cyclophosphamide, etoposide, cladribine and cytarabine but the evidence for their use is limited (Gotlib, 2014).

Monoclonal antibodies.
Anti-interleukin 5 monoclonal antibodies: IL5 is the primary cytokine involved in eosinophil development and is frequently elevated in patients with HES (Owen et al, 1989). Two monoclonal anti-IL5 antibodies have shown promising efficacy: mepolizumab, a fully humanised murine antibody, and reslizumab, a humanised rat antibody. Mepolizumab has shown efficacy in steroid-refractory (Plotz et al, 2003) and steroid-dependent HES (Rothenberg et al, 2008; Ogbogu et al, 2009). Roufosse et al (2010, 2013) reported that patients receiving the highest doses of prednisolone at the outset responded better to mepolizumab than those on lower doses. However patients with the greatest fall in eosinophil counts did not experience fewer HES-related symptoms. The drug was well tolerated. There is currently no evidence on its effectiveness in improving end-organ damage in HES. It should be noted that mepolizumab has recently been approved for use in refractory asthma in Europe and the USA but the approved dose in this setting is significantly lower than that used in published HES studies and is unlikely to be effective for patients with HES. There are fewer data on reslizumab. Klion et al (2004) found that two of four HES patients responded to monthly reslizumab infusions but relapsed following cessation of therapy. Response was not predicted by FIP1L1-PDGFRA status or baseline IL5 levels.

- Alemtuzumab, an anti-CD52 monoclonal antibody, should be considered for patients with severe idiopathic HES unresponsive to other therapies, and may be useful in patients with idiopathic HES-associated cardiac and cerebral dysfunction. (**Grade 2B**)

  Alemtuzumab: Two initial reports indicate that alemtuzumab may induce clinical and haematological remissions in patients with HES unresponsive to corticosteroids, hydroxycarbamide, interferon and imatinib (Pitini et al, 2004; Sefcick et al, 2004; Strati et al, 2013). Patients relapsing after therapy may achieve durable responses following retreatment with alemtuzumab. The principal complications were infections (including cytomegalovirus reactivation) and infusion reactions. Two case reports suggest that alemtuzumab can reverse established cardiac and cerebral dysfunction in patients with FIP1L1-PDGFRA-negative HES (Perini et al, 2009; Syed et al, 2012).

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Role of haemopoietic stem cell transplantation

- HSCT should be considered for cases with clonal eosinophilia with FGFR1 rearrangement, patients with chronic eosinophilic leukaemia, not otherwise specified and those HES patients refractory to or intolerant of both conventional TKI therapy and experimental medical therapy, where available, or who display progressive end organ damage (**Grade 2C**).

Allogeneic HSCT has been performed in a small number of patients with refractory or debilitating HES that was idiopathic or ill-defined and prolonged remissions have been reported (Ueno et al, 2002; Cooper et al, 2005). A lack of clinical trials, small numbers reported and clinical heterogeneity make it impossible to offer definitive recommendations. Although both myeloablative and reduced intensity conditioning regimens have been used, there remains insufficient evidence to give recommendations on conditioning regimen or intensity (Juvonen et al, 2002; Ueno et al, 2002; Cooper et al, 2005; Halaburda et al, 2006).
Cases of eosinophilia associated with FGFR1 rearrangement have a poor prognosis and intensive AML-type induction treatment followed by HSCT may be the best option. Because of the poor prognosis of CEL, NOS (Helbig et al, 2012) this approach could also be justified in these cases.
HSCT should also be considered for those HES patients refractory to or intolerant of both conventional TKI therapy and experimental medical therapy, where available, or who display progressive end organ damage (Fathi et al, 2014).

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National Comprehensive Cancer Network (NCCN), 2021 [2,3].

Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes; Version 4.2021

Zielsetzung/Fragestellung

The NCCN Guidelines for Myeloid/Lymphoid Neoplasms with Eosinophilia and TK Fusion Genes include recommendations for the diagnosis, staging, and treatment of any one of the MLN-Eo associated with a TK fusion gene included in the 2017 WHO Classification, as well as MLN-Eo with a FLT3 or ABL1 rearrangement.

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund fehlender aktueller höherwertiger Evidenz wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: keine Betroffenen beteiligt;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz unklar;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig, die Verknüpfung mit der zugrundeliegenden Evidenz ist nur indirekt über den Hintergrundtext zu den Empfehlungen möglich;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

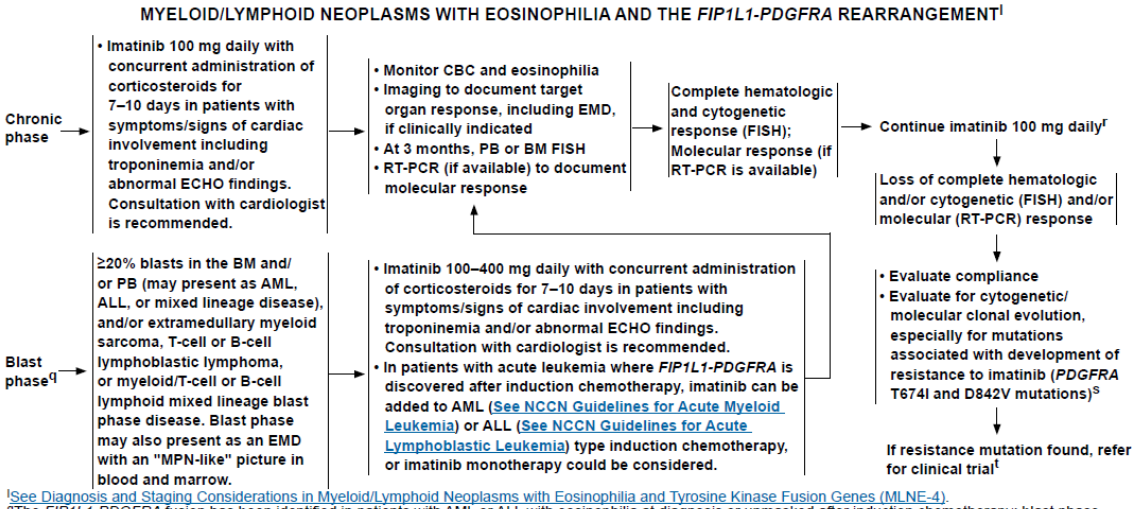
- Prior to the development of NCCN Guidelines for Myeloid/Lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes, an electronic search of the PubMed databse was performed to obtain key literature in the last 10 years.

LoE / GoR

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

All recommendations are category 2A unless otherwise indicated.

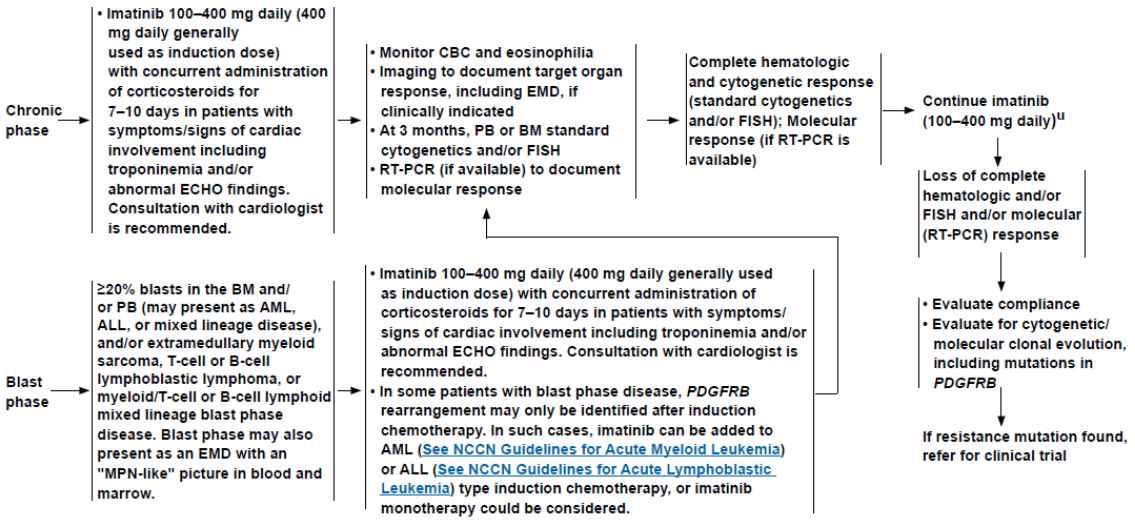
Empfehlungen



[l]See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).
[q]The *FIP1L1-PDGFRA* fusion has been identified in patients with AML or ALL with eosinophilia at diagnosis or unmasked after induction chemotherapy; blast phase disease may also develop as progression from chronic phase disease due to cytogenetic/molecular clonal evolution, including mutations associated with development of resistance to imatinib (*PDGFRA* T674I and D842V).
[r]Complete hematologic response (CHR) by 1 month and complete cytogenetic response (CCyR; FISH) by 3 months is achieved in a vast majority of patients. In patients with ongoing CHR and CCyR (FISH), maintenance doses of imatinib as low as 100–200 mg, weekly, have been used with sustained responses; continue to monitor hematologic and cytogenetic response (by FISH) every 3–6 months, and if available, molecular response by RT-PCR at these time points. Helbig G, et al. Br J Haematol 2008;141:200-204.
[s]*PDGFRA* T674I and D842V mutations are resistant to imatinib.
[t]Avapritinib is approved for advanced systemic mastocytosis (SM) (aggressive SM [ASM], SM with an associated hematologic neoplasm [SM-AHN], and mast cell leukemia [MCL]) and also for unresectable or metastatic gastrointestinal stromal tumors (GISTs) harboring a *PDGFRA* exon 18 mutation, including D842V mutations. This suggests a possible role for avapritinib in patients with *FIP1L1-PDGFRA*–positive myeloid/lymphoid neoplasms with eosinophilia harboring *PDGFRA* D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MLNE-5

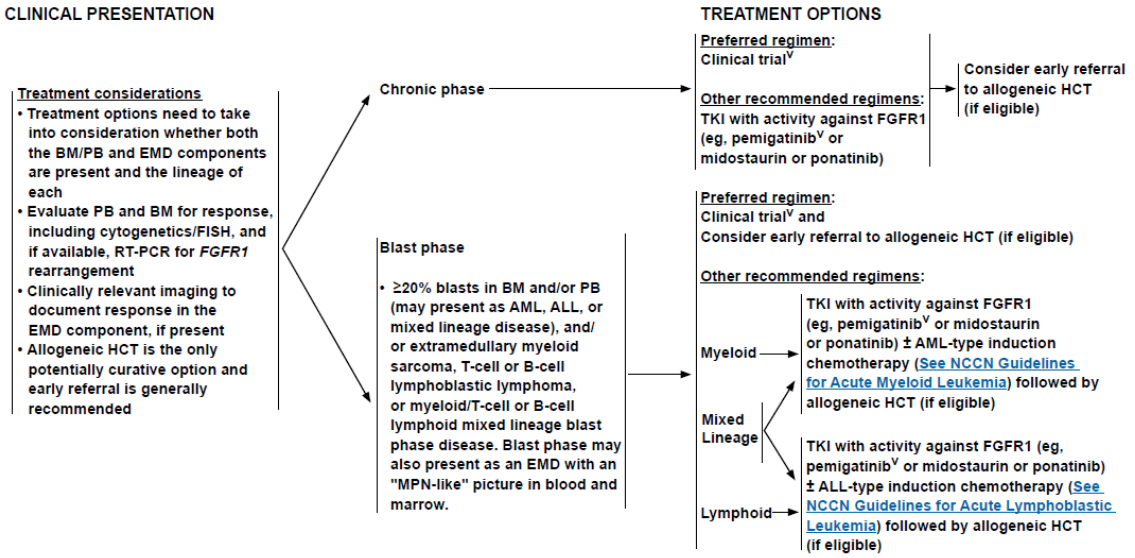


[l]See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).
[o]Eosinophilia is not invariably present.
[u]CHR by 1 month and CCyR (standard cytogenetics and/or FISH) by 3 months is achieved in a vast majority of patients. Continue to monitor hematologic and cytogenetic response (by FISH) every 3–6 months, and if available, molecular response by RT-PCR. Reduction of imatinib to 100 mg daily can be considered after achievement of CHR and complete cytogenetic/FISH response.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MLNE-6

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *FGFR1* REARRANGEMENT[l,o]

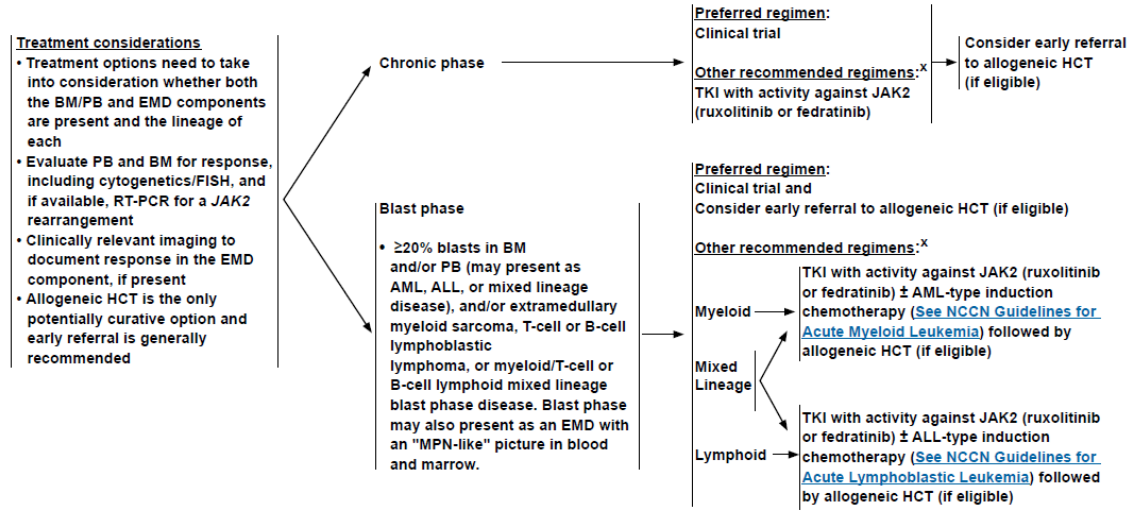


[l] See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).
[o] Eosinophilia is not invariably present.
[v] Pemigatinib (FGFR1, 2, and 3 inhibitor) is approved for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma and a *FGFR2* fusion or other rearrangement, as detected by an FDA-approved test. Pemigatinib has received orphan drug designation for the treatment of patients with myeloid/lymphoid neoplasms with eosinophilia and *FGFR1* rearrangement and is currently being evaluated in a clinical trial for this indication. A clinical trial of pemigatinib is preferred (if available), rather than off-label use (Hoy SM. Drugs 2020;80:923-929; Verstovsek S, et al. Blood 2018;132:Abstract 690).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MLNE-7

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *JAK2* REARRANGEMENT[l,n,o,w]

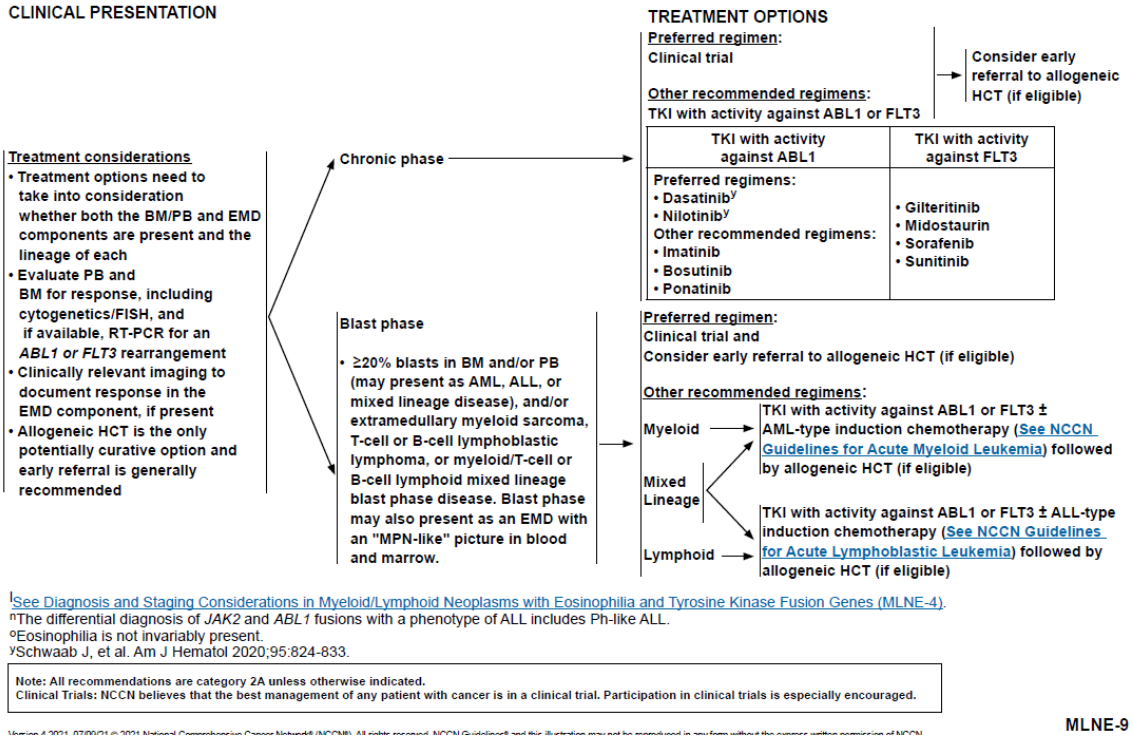


[l] See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).
[n] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.
[o] Eosinophilia is not invariably present.
[w] Only myeloid/lymphoid neoplasms with *PCM-JAK2* are included in the 2017 WHO classification as a provisional entity (see MLNE-B). Other *JAK2* rearrangements are considered variants.
[x] Ruxolitinib is most commonly used (Rumi E, et al. J Clin Oncol 2013;31:e269-e271; Rumi E, et al. Ann Hematol 2015;94:1927-1928; Schwaab J, et al. Ann Hematol 2015;94:233-238; Schwaab J, et al. Am J Hematol 2020;95:824-833). Fedratinib may be an appropriate alternative treatment option.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MLNE-8

MYELOID/LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND *ABL1 OR FLT3* REARRANGEMENT[l,n,o]



[l] See Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (MLNE-4).
[n] The differential diagnosis of *JAK2* and *ABL1* fusions with a phenotype of ALL includes Ph-like ALL.
[o] Eosinophilia is not invariably present.
[y] Schwaab J, et al. Am J Hematol 2020;95:824-833.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MLNE-9

NGS studies are not broadly available and currently the prognostic impact and pathogenicity of additional mutations detected by NGS have not been established. Further studies are needed to determine the impact of these novel mutations on disease course.

Treatment Considerations

All patients should be evaluated and managed by a multidisciplinary team (including engagement of other sub-specialists based on clinical presentation and organ involvement) in specialized centers.

Assessment for clinical situations that may require urgent intervention is recommended for all patients. Immediate institution of oral or high-dose IV corticosteroids may be necessary as clinically indicated, especially in patients in whom eosinophil-mediated cardiac damage/heart failure is present or suspected.

As noted earlier, consultation with an infectious disease specialist is recommended as clinically indicated for the management of infectious disease-related complications.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *PDGFRA* or *PDGFRB* Rearrangement

Imatinib has resulted in high rates of durable hematologic and molecular responses in the vast majority of patients with MLN-Eo and *PDGFRA* or *PDGFRB* rearrangement.[19,25,33,72-84] Concurrent administration of corticosteroids for 7 to 10 days and consultation with a cardiologist is recommended for patients with symptoms/signs of cardiac involvement including troponinemia, elevated NT-proBNP, and/or abnormal ECHO findings.[75]

Imatinib 100 mg daily is the recommended dose for induction therapy for chronic phase disease in patients with *FIP1L1-PDGFRA* rearrangement. Imatinib 100 mg to 400 mg daily is the recommended dose for chronic

Continuation of imatinib at the initial dose is recommended for patients achieving a complete response (CHR, CCyR, or complete molecular response [CMR]). While low doses of 100 mg to 200 mg daily have been sufficient to maintain molecular remission in the majority of patients with *FIP1L1-PDGFRA* rearrangement, and in some cases this dose range has been used only once weekly,[74] higher doses (maximum of 400 mg daily) may be required for some patients.[75,76]

Monitoring hematologic response, cytogenetic response (FISH), and molecular response (if RT-qPCR is available) every 3 and 6 months is recommended for patients achieving a durable complete response to initial treatment. Clinical trial and/or early referral to allogeneic HCT should be considered for patients with loss of response. Evaluation of patient compliance or drug interactions is recommended prior to initiation of additional treatment for patients with loss of response.

Acquired resistance to imatinib mediated by *PDGFRA* T674I and D842V mutations has been reported in few patients with blast phase disease.[73,86] Nilotinib, ponatinib, and sorafenib have shown limited activity in patients with *PDGFRA* T674I and D842V mutations.[86-89] *PDGFRB* T681I has been shown to confer resistance to imatinib in vitro, but has not yet been identified in patients treated with imatinib; acquired resistance to imatinib mediated by other *PDGFRB* mutations has been described only in two case reports.[90-92] Evaluation for cytogenetic/molecular clonal evolution can identify *PDGFRA* (T674I and D842V) or *PDGFRB* mutations conferring resistance to imatinib in patients with loss of response. Referral to clinical is recommended, if resistance mutation found.

Avapritinib is approved for advanced SM (aggressive SM, SM with an associated hematologic neoplasm, and mast cell leukemia) and also for unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring a *PDGFRA* exon 18 mutation, including D842V mutations.[93-97] This suggests a possible role for avapritinib in patients with MLN-Eo and

In the absence of a suitable clinical trial, TKI ± induction chemotherapy followed by allogeneic HCT is the appropriate treatment approach.

phase in patients with *PDGFRB* rearrangement, although 400 mg daily is generally used as the induction dose. Reduction to 100 mg daily can be considered after achievement of complete hematologic response (CHR) and complete cytogenetic response (CCyR).

Blast phase disease may present either as de novo or as disease progression from chronic phase due to cytogenetic/molecular clonal evolution, including *PDGFRA* mutations associated with development of resistance to imatinib including T674I or D842V.[73]

Imatinib monotherapy (100–400 mg daily) is recommended for blast phase disease (400 mg daily is generally used as the induction dose in patients with *PDGFRB* rearrangement). Durable remissions are only rarely achieved with induction chemotherapy or allogeneic hematopoietic cell transplant (HCT). In instances when *FIP1L1-PDGFRA* or a *PDGFRB* rearrangement is identified only after the initiation of induction chemotherapy, imatinib should be added to induction chemotherapy (ALL-type chemotherapy for lymphoid blast phase and AML-type chemotherapy for myeloid blast phase), or a return to imatinib monotherapy may also be considered.[25,78]

Monitoring Response and Additional Treatment

CHR (defined as the normalization of peripheral blood counts and eosinophilia) by 1 month and CCyR by 3 months is achieved in a vast majority of patients.[85]

Monitoring blood counts (CBC and eosinophilia), imaging to document target organ response (as clinically indicated), and peripheral blood or bone marrow evaluation (FISH for *FIP1L1-PDGFRA* since standard karyotyping cannot detect the fusion; standard cytogenetics and/or FISH for *PDGFRB*) are recommended at 3 months after initiation of imatinib. RT-PCR (if available) can be considered to document molecular response.

MS-11

PDGFRA rearrangement harboring *PDGFRA* D842V mutation resistant to imatinib. If this mutation is identified, a clinical trial of avapritinib is preferred (if available), rather than off-label use.

The feasibility of discontinuation of imatinib in patients with MLN-Eo and *PDGFRA* rearrangement who have achieved CMR has been demonstrated mostly in retrospective studies in a limited number of patients.[33,72,98,99] There is substantial variability in the relapse-free survival rates (57%–91% at 12 months; 42%–65% at 24 months), although molecular remissions have been re-established after restarting imatinib in most patients experiencing relapse after discontinuation of imatinib. The feasibility of discontinuation of imatinib in patients with MLN-Eo and a *PDGFRB* rearrangement has not been evaluated. At the present time, there are no definite criteria to identify patients suitable for discontinuation of imatinib and it is therefore not recommended outside the context of clinical trials.

Myeloid/Lymphoid Neoplasms with Eosinophilia and *FGFR1 or JAK2 or FLT3* or *ABL1* Rearrangement

MLN-Eo with the above-mentioned TK fusion gene rearrangements are generally associated with an aggressive clinical course, relapse, or disease progression to blast phase and allogeneic HCT is the only potentially curative option.[9,10,28,31,100]

Clinical trial is the preferred treatment option for patients with chronic phase disease. In the absence of a clinical trial, patients with chronic phase disease can be treated with TKI monotherapy. However, early referral to allogeneic HCT should be considered for eligible patients, since TKI therapy alone does not result in durable remissions.

Clinical trial and early consideration of allogeneic HCT for eligible patients is the preferred treatment approach for patients with blast phase disease.

MS-12

The selection of chemotherapy for blast phase disease should be based on the cell lineage (ALL-type chemotherapy for lymphoid blast phase and AML-type chemotherapy for myeloid blast phase; either of these induction chemotherapy regimens can be considered for mixed-lineage blast phase disease).

TKIs with activity against *FGFR1*, *JAK2*, *FLT3* or *ABL1*, are listed in the table below. Given the rare nature of this disease, available evidence is mainly from case reports and/or their potential clinical activity is extrapolated from other diseases with the same target. Although TKI ± induction chemotherapy does not result in long-term disease control, it may be of potential benefit when used as a bridge to allogeneic HCT for disease cytoreduction prior to transplantation.[27,100-103]

TKI with Activity Against *FGFR1*	TKI with Activity Against *JAK2*	TKI with Activity Against *FLT3*	TKI with Activity Against *ABL1*[a]
Pemigatinib[b,104,105] Midostaurin[106] Ponatinib[27,89,102,107,108]	Ruxolitinib[103,109-111] Fedratinib[c]	Gilteritinib[c] Midostaurin[c] Sorafenib[101,112] Sunitinib[112]	Dasatinib[103] Nilotinib[103] Imatinib[103] Bosutinib[c] Ponatinib[c]

a.Dasatinib or nilotinib are more effective than imatinib to induce durable complete remissions in patients with *ETV6-ABL1* fusion gene.[103]
b.Pemigatinib (FGFR inhibitor) is approved for the treatment of previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement, (as detected by an FDA-approved test). It has received orphan drug designation for the treatment of patients with MLN-Eo and *FGFR1* rearrangement. It is currently being evaluated in a clinical trial for this indication and a clinical trial of pemigatinib is preferred (if available), rather than off-label use.
c.The inclusion of these TKIs is based on the extrapolation of data from MPN (fedratinib for MF) and other myeloid neoplasms (gilteritinib and midostaurin for AML; bosutinib and ponatinib for CML).

Clinically relevant imaging studies to document response in the EMD component and evaluation of peripheral blood or bone marrow (FISH or cytogenetics) and RT-PCR (if available) for specific TK fusion gene rearrangement to document response (hematologic, cytogenetic, or molecular response) should be considered for all patients after initiation of treatment. However, it should be noted that there are no consensus response criteria for assessment of response.

Monitoring minimal residual disease (MRD) after allogeneic HCT and maintenance therapy with TKI (eg, ponatinib) or hypomethylating agent (eg, 5-azacytidine) has been shown to be effective for MLN-Eo with *FGFR1* rearrangement in single case reports.[108,113] The role for TKI as maintenance therapy following allogeneic HCT has not been systematically evaluated but may be considered in patients felt to be at high risk for relapse. Additional studies are needed to confirm the efficacy of this treatment approach.

MS-14

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2021) am 24.09.2021

#	Suchfrage
1	[mh "Hypereosinophilic Syndrome"]
2	(hypereosinophil* OR hyper-eosinophil*):ti,ab,kw
3	Loeffler*:ti,ab,kw
4	(Eosinophil* AND (leukemia* OR leukaemia*)):ti,ab,kw
5	(Gleich* AND syndrom*):ti,ab,kw
6	[mh ^Eosinophilia]
7	eosinophilia*:ti,ab,kw
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	#8 with Cochrane Library publication date from Sep 2016 to present

Systematic Reviews in Medline (PubMed) am 24.09.2021

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

#	Suchfrage
1	hypereosinophilic syndrome[mh]
2	(hypereosinophil*[tiab] OR hyper-eosinophil*[tiab])
3	loeffler*[tiab]
4	Eosinophil*[tiab] AND (leukemia*[tiab] OR leukaemia*[tiab])
5	Gleich*[tiab] AND syndrom*[tiab]
6	Eosinophilia[mh:noexp]
7	eosinophilia*[tiab]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw]

#	Suchfrage
1	hypereosinophilic syndrome[mh]
2	(hypereosinophil*[tiab] OR hyper-eosinophil*[tiab])
3	loeffler*[tiab]
4	Eosinophil*[tiab] AND (leukemia*[tiab] OR leukaemia*[tiab])
5	Gleich*[tiab] AND syndrom*[tiab]
	OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
10	(#9) AND ("2016/09/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 24.09.2021

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

#	Suchfrage
1	hypereosinophilic syndrome[mh]
2	(hypereosinophil*[tiab] OR hyper-eosinophil*[tiab])
3	loeffler*[tiab]
4	Eosinophil*[tiab] AND (leukemia*[tiab] OR leukaemia*[tiab])
5	Gleich*[tiab] AND syndrom*[tiab]
6	Eosinophilia[mh:noexp]
7	eosinophilia*[tiab]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
10	(#9) AND ("2016/09/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 27.09.2021

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

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

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

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

Referenzen

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2. **National Comprehensive Cancer Network (NCCN).** Myeloid/Lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes; Evidence Blocks; Version 4.2021 [online]. Plymouth Meeting (USA): NCCN; 2021. [Zugriff: 24.09.2021]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/mlne.pdf.

3. **National Comprehensive Cancer Network (NCCN).** Myeloid/Lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes; Version 4.2021 [online]. Plymouth Meeting (USA): NCCN; 2021. [Zugriff: 24.09.2021]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/mlne.pdf.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021