Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-012 Ibrutinib

Stand: Februar 2019

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

Ibrutinib
[in Kombination mit Rituximab zur Behandlung des Morbus Waldenström]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Autologe Stammzelltransplantation - Allogene Stammzelltransplantation - Plasmapherese
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Ibrutinib, Beschluss vom 21. Juli 2016 Beschluss über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use Fludarabin, Beschluss vom 17. Februar 2011 *<u>Nicht zugelassenes Anwendungsgebiet (Off-Label- Indikation):</u>* *Fludarabin in Kombination mit Cyclophosphamid, Mitoxantron und Rituximab (R-FCM) bei geeigneten Patienten mit niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe (CD20 positive NHL, u. a. lymphozytisch, lymphoplasmozytisch, lymphoplasmazytoid, follikulär Grad 1 oder 2, Mantelzell, Marginalzonen, nicht multiples Myelom, nicht Haarzellleukämie) und Resistenz auf CHOP (mit oder ohne Rituximab)*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ibrutinib L01XE27 Imbruvica®	<u>Zugelassenes Anwendungsgebiet:</u> Imbruvica® in Kombination mit Rituximab ist indiziert zur Behandlung erwachsener Patienten mit Morbus Waldenström.
Bendamustin L01AA09 Levact®	Primärtherapie bei chronischer lymphatischer Leukämie (Binet-Stadium B oder C) bei Patienten, bei denen eine Fludarabin-Kombinations-Chemotherapie ungeeignet ist. Monotherapie bei indolenten Non-Hodgkin-Lymphomen bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab oder mit einer Rituximab-haltigen Therapie.
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (CLL), niedrig maligne Non-Hodgkin-Lymphome, Waldenström Makroglobulinämie
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: − Non-Hodgkin-Lymphome (in Abhängigkeit vom histologischen Typ und vom Krankheitsstadium auch als Monotherapie) − […]
Ibrutinib L01XE27 Imbruvica®	IMBRUVICA als Einzelsubstanz ist indiziert zur Behandlung erwachsener Patienten mit Morbus Waldenström (MW), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten, die für eine Chemo-Immuntherapie nicht geeignet sind.
Dexamethason H02AB02 Dexamethason acis®	- Palliativtherapie maligner Tumoren - […]

II. Zugelassene Arzneimittel im Anwendungsgebiet

Prednisolon H02AB06 Dermosolon®	Hämatologie/Onkologie: […] Akute lymphoblastische Leukämie (DS: e) Morbus Hodgkin (DS: e) Non-Hodgkin-Lymphome (DS: e) chronisch lymphatische Leukämie (DS: e) Morbus Waldenström (DS: e) multiples Myelom (DS: e) Hyperkalzämie bei malignen Grunderkrankungen (DS: c bis a) […]
Prednison H02AB07 Cutason®	Hämatologie/Onkologie: […] Akute lymphoblastische Leukämie (DS: e), Morbus Hodgkin (DS: e), Non-Hodgkin-Lymphome (DS: e), Chronisch lymphatische Leukämie (DS: e), Morbus Waldenström (DS: e), Multiples Myelom (DS: e), Hyperkalzämie bei malignen Grunderkrankungen (DS: c bis a) […]
Cytarabin L01BC01 ARA-cell®	ARA-cell® 100 mg/ml wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: − refraktären Non-Hodgkin-Lymphomen
Doxorubicin L01DB01 Adrimedac®	Non-Hodgkin-Lymphome
Trofosfamid L01AA07 Ixoten®	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet.
Vinblastin L01CA01 Vinblastinsulfat Teva®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: − maligne Non-Hodgkin-Lymphome
Vincristin L01CA02 Vincristinsulfat-Teva®	Vincristinsulfat-Teva® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: − malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen

Quellen: AMIS-Datenbank, Fachinformationen

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CLB	Chlorambucil
CLL	Chronische lymphatische Leukämie
CR	Complete response
CT	Clinical trial
DRC	Dexamethason, Rituximab, Cyclophosphamid
FCR	Fludarabine, Cyclophosphamide, Rituximab
FL	Follikuläres Lymphom
Fluda	Fludarabin
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IWWM	International Workshop on Waldenström macroglobulinemia
KI	Konfidenzintervall
LL	Lymphoplasmacytic lymphoma
LoE	Level of Evidence
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin Lymphom
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall response rate
PR	Partial response
R	Rituximab
RR	Response rate
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database

VGPR	Very good partial response
WHO	World Health Organization
WM	Waldenström macroglobulinemia

Indikation

Ibrutinib in Kombination mit Rituximab ist indiziert zur Behandlung erwachsener Patientinnen und Patienten mit Morbus Waldenström.

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Morbus Waldenström* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.01.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 147 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 6 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Ergebnisse

G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2016 [3].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Juli 2016 - Ibrutinib

Anwendungsgebiet (laut Zulassungen vom 21.10.2014 und 03.07.2015):

IMBRUVICA® ist indiziert zur Behandlung erwachsener Patienten mit Morbus Waldenström, die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinientherapie bei Patienten die für eine Chemo-Immuntherapie nicht geeignet sind. (entspricht Anwendungsgebiet III des Beschlusses)

Zweckmäßige Vergleichstherapie

Eine patientenindividuelle optimierte Therapie nach Maßgabe des Arztes, grundsätzlich unter Beachtung des Zulassungsstatus, sowie unter Beachtung von Anlage VI der Arzneimittelrichtlinie (Off-Label Use).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

Cochrane Reviews

Zur Fragestellung wurden keine Cochrane Reviews identifiziert.

Systematische Reviews

Canadian Agency for Drugs and Technologies in Health (CADTH), 2016 [1].

Ibrutinib (Imbruvica) for Waldenström's Macroglobulinemia

Pan-Canadian Oncology Drug Review

Final Clinical Guidance Report

Fragestellung

To evaluate the safety and efficacy of Ibrutinib on patient outcomes in the treatment of adults with Waldenström's Macroglobulinemia who have received one prior therapy.

Methodik

Population:

Adult patients with Waldenström's Macroglobulinemia who have received at least one prior therapy

Subgroups of interest: symptomatic versus asymptomatic patients

Intervention:

Ibrutinib monotherapy

Komparator:

All appropriate multiagent chemotherapy regimens including but not limited to:

1.1 cyclophosphamide, vincristine, prednisone, with/without rituximab

1.2 cyclophosphamide, dexamethasone, rituximab

1.3 bendamustine, rituximab

1.4 regimens including cladribine ore fludarabine

1.5 chlorambucil alone

1.6 rituximab alone

Endpunkte:

OS, PFS, response, duration of response, time to next therapy, QoL, disease symptoms including neuropathy, headache, confusion, shortness of breath, Hb levels, (S/WD)AEs, AEs of interest including major bleeding, arterial fibrillation, diarrhoea, skin rash

Recherche/Suchzeitraum:

The search is considered up to date as of August 2, 2016.

Qualitätsbewertung der Studien:

SIGN-50 checklist

Additional limitations and sources of bias were identified by the pCODR review team.

Ergebnisse

Anzahl eingeschlossener Studien:

11 reports included presenting data from 2 unique studies: PCYC-1118E und PCYC-1127 (arm C)

Charakteristika der Population:

adult patients with Waldenström's Macroglobulinemia, required treatment according to recent guidelines, maximum ECOG 2, median ages 63 and 67 years

received oral ibrutinib 420 mg daily until disease progression or unacceptable toxicity

baseline characteristics differ between studies: in PCYC-1118E better ECOG, lower number of previous therapies for MW; in PCYC-1127 patients with disease refractory to the last prior rituximab-containing therapy

Qualität der Studien:

The main limitations of the included studies are related to their non-randomized, open-label study designs. While PCYC-1127 was a RCT with three arms, data are only available for Arm C (ibrutinib monotherapy). For both studies, making inferences from the results of non-comparative study or the single arm of an RCT is challenging and the efficacy and harms of Ibrutinib in WM relative to other agents is uncertain. Results for study PCYC-1127 were presented only in abstract form and were from an interim analysis; the data will need to be reviewed as full results become available in the future.

Studienergebnisse:

no data on OS reported

Some QoL data were provided by the manufacturer, but it was not possible to assess the statistical or clinical significance of these data.

study PCYC-1118E

1.7 SAEs occurring more than once: thrombocytopenia (n=2), pyrexia (n=3), pneumonia (n=5)

1.8 SAEs that occurred once: febrile neutropenia, neutropenia, atrial fibrillation, sinus tachycardia, chills, malaise, cholecystitis, cellulitis, herpes zoster, influenza, pleural infection, streptococcal endocarditis, upper respiratory tract infection, post-procedure hematoma, dehydration, B-cell lymphoma, myelodysplastic syndrome, syncope, pleural diffusion.

1.9 one death due to worsening of pleural effusion 22 days after the last dose of study drug, attributed to disease progression

1.10 AE rated grade 3 or higher: a half (n=32) of the patients

1.11 haemorrhagic AE of any grade: 44,4% of the patients

1.12 At median treatment duration of 19,1 month, there was one report of grade 3 hematoma (post procedural bleeding event), but no grade 4 bleeding events.

1.13 AEs leading to ibrutinib discontinuation (each occurred once): arterial fibrillation , B-cell lymphoma, myelodysplatic syndrome, pleural effusion, post procedural haematoma and thrombocytopenia

In study PCYC-1127, SEAs occurred in 10 patients (32%).

Anmerkung/Fazit der Autoren

The Clinical Guidance Panel concluded that there is a net clinical benefit to treatmant with ibrutinib in patients with relapsed or refractory WM. This conclusion is based on the high

response rate and long progression-free survival reported in a phase II study, supported by results from a three-arm trial reports in abstract form. The toxicity profile of ibrutinib in this patient population is favourable and side effects are manageable.

Santos-Lozano A et al., 2016 [6].

Response rate to the treatment of Waldenstrom macroglobulinemia: A meta-analysis of the results of clinical trials

Fragestellung

The purpose of the present meta-analysis was toassess the effectiveness of the different WM treatments tested in published trials by comparing RR, CR, VGPR and PR results.

Methodik

Population:

patientswith WM as the study participants

Intervention:

not defined

Komparator:

not defined

Endpunkte:

treatment out-come provided as RR

Recherche/Suchzeitraum:

up to January 30, 2015

Qualitätsbewertung der Studien:

Newcastle-Ottawa quality assessment scale for nonrandomised studies, including case-control and cohort studies

Ergebnisse

Anzahl eingeschlossener Studien:

46 studies (corresponding to a total of 1 409 patients)

7, 7 and 8 trials assessed monotherapy with rituximab, fludarabine or cladribine, respectively, and 24 trials examined the outcomes of combined therapy as treatment for WM.

Charakteristika der Population:

trials heterogeneous in terms of sample size (n ranged from 3 to 182)

in most trials, more men than women included

age ranges: wide across all trials, young/middle aged and elderly individuals included

1.14 39–90 years for the rituximab trials,

1.15 34–79 years for the fludarabine trials,

1.16 35–88 years for the cladribinetrials,

1.17 30–89 years for the treatment combinations trials

Investigated interventions: Rituximab monotherapy, Fludarabine monotherapy, Cladribine monotherapy, combined treatments, Rituximab + cyclophosphamide/dexamethasone vs.

the rest of combinations, Rituximab + bortezomib/dexamethasone vs. other the rest of combinations, Rituximab + cladribine

doses of fludarabine and cladribine varied slightly (25, 30 or 40 mg/m2 and 0,10; 0,12 or 0,14 mg/kg, respectively), the same rituximab dose (375 mg/m^2) used in all trials

Qualität der Studien:

All trials obtained at least 7 points on the Newcastle-Ottawa quality assessment scale

Studienergebnisse:

greater response to treatment produced with a combination of 2+ drugs (RR = 73%; 95%CI: 62, 83; p < 0.01) than monotherapy with rituximab (RR = 44%;95%CI: 34, 55; p < 0.01) or a purine analogue [61% (95%CI: 43, 78; p < 0.01) for cladribine and 53% (95%CI: analysis 34, 72; p < 0.01) for fludarabine]

combination rituximab + cladribine particularly effective (RR = 87%; 95%CI: 78, 94; p < 0.01), slightly more effective than rituximab + bortezomib/dexamethasone (RR = 84%; 95%CI: 79, 88; p < 0.01) and rituximab + cyclophosphamide/dexamethasone [RR = 81% (95%CI:72, 88; p < 0.01)]

results in overall agreement with treatment recommendations from the seventh International Workshops on WM

findings limited by the fact that we could not analyse progression-free survival (PFS)

phase II/III trials are needed to corroborate promising recent findings with bendamustine and carfilzomib and further research are needed to standardize recommendations based on maximum treatment efficacy combined with lowest toxicity, differentiation between first vs second line treatment, or long-term follow up after treatment

Anmerkung/Fazit der Autoren

In conclusion, patients with WM show a better response to combination therapy than monotherapy. Among the drug combinations tested to date, rituximab-based therapy (especially rituximab + cladribine) seems to be especially effective, although the rituximab + bortezomib/dexamethasone combination, which is one of the main therapies recommended by the IWWM-7 consensus (Dimopoulos et al., 2014) also showed a good response to treatment (RR = 84%).

Kommentare zum Review

- *viele Wirkstoffe nicht oder „off label“ zugelassen*
- *Validität des Endpunktes Ansprechen als Surrogatparameter unklar*
- *None of the authors have any conflict of interest.*
- *Finanzierung der Arbeit unklar.*

Lepretre S et al., 2016 [4].

Systematic review of the recent evidence for the efficacy and safety of chlorambucil in the treatment of B-cell malignancies

Fragestellung

This systematic review collates all the empirical evidence on the efficacy and safety of CLB used alone or in combination with other treatments in CLL patients and in patients with low-grade NHLs.

Methodik

Population:

First line treatment of patients with WM

Intervention:

with at least one group using CLB

Komparator:

no limitation

Endpunkte:

no limitation

Recherche/Suchzeitraum:

This work was conducted from October 2013 to June 2014

Qualitätsbewertung der Studien:

not mentioned

Ergebnisse

Anzahl eingeschlossener Studien:

search results revealed 59 articles and 6 studies were selected and summarized

Charakteristika der Population:

patients suffered mainly from FL (three trials), MCL (two trials), LL (two trials), MALT or well-differentiated lymphoma (three trials) or WM (one trial)

Referenzen

[24] Leblond V, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenstro¨m macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. J Clin Oncol 2013; 31: 301–307.

Number of patient randomized: Fludarabine n = 209; CLB n = 209

patients main inclusion criteria: 339 untreated patients with WM, 37 with non-MALT MZL, 38 with LL

description of patients at baseline: median age 68 y

Qualität der Studien:

RCT, open-label

critical appraisal not available

Studienergebnisse:

efficacy

1.18 patients receiving CLB had a lower ORR (35.9 vs. 45.6%) ($p = 0.07$) than those treated with fludarabine

1.19 statistical differences observed between the groups in PFS ($p = 0.015$), duration of response ($p = 0.0024$) and OS ($p = 0.014$)

Safety (Grade III–IV AEs)

1.20 Neutropenia: Fluda 36%; CLB 17.8% ($p < 0.001$)

1.21 Second malignancies (6-year cumulative incidence rate): CLB 20.6%; Fluda 3.7% ($p = 0.001$)

Anmerkung/Fazit der Autoren

In conclusion, our review has shown that the main advantage of CLB is its low level of toxicity in comparison with PNAs such as fludarabine, in CLL, WM, non-MALT- MZL and LL. … In FL or MCL and WM, CLB results in a lower response rate than other treatments, but remains an alternative for unfit patients.

Kommentare zum Review

- *Achtung: „risk of bias" der eingeschlossenen Studien nicht systematisch bewertet*
- *Disclosure forms provided by the authors are available with the full text of this article*
- *Finanzierung der Arbeit unklar.*

Leitlinien

Gavriatopoulou M et al., 2018 [2].

European Myeloma Network (EMN)

European myeloma network recommendations on diagnosis and management of patients with rare plasma cell dyscrasias

Ziel

… to provide useful recommendations on diagnosis and management of these entities [Anmerkung: Waldenström's macroglobulinemia (WM), primary systemic AL-amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), POEMS-syndrome, and primary plasma cell leukemia (PPCL)]

Methodik

Grundlage der Leitlinie:

repräsentatives Gremium (ohne Patientenvertretung);

Interessenkonflikte dargelegt; finanzielle Unabhängigkeit unklar;

systematische Suche, Auswahl und Bewertung der Evidenz wahrscheinlich;

informale Konsensusprozesse beschrieben; ohne externes Begutachtungsverfahren;

Empfehlungen der Leitlinie sind eindeutig; Verbindung zu der zugrundeliegenden Evidenz indirekt (im Hintergrundtext) dargestellt;

Regelmäßige Überprüfung der Aktualität unklar

Recherche/Suchzeitraum:

until 28th February 2018

LoE (Power of evidence - A: high, C: low)

A. Consistent evidence from systemic reviews of high quality randomized studies or from high quality observational studies

B. Evidence from randomized and observational studies with important methodological flaws

C. Evidence from randomized and observational studies with major methodological flaws or other sources of evidence (eg. Case series)

GoR (Benefit/risks of procedure)

1. Evidence strongly suggests that the benefit of the procedure outweighs potential risks or risks of the procedure outweigh potential benefits

2. Evidence suggest that the benefit and risk of a procedure is finely balanced or uncertain

Sonstige methodische Hinweise

Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used for the grading of the recommendations

Recommendations on management of newly diagnosed (ND), symptomatic WM patients

Empfehlung 1 (Empfehlungsgrad 1B)

Rituximab monotherapy can be considered for WM patients with immunologic disorders secondary to WM or for frail patients who are less likely to tolerate chemotherapy.

Referenzen

5. Dimopoulos MA, et al. Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood. 2014;124:1404–11.
6. Treon SP, et al. CD20-directed antibody-mediated immunotherapy induces responses and facilitates hematologic recovery in patients with Waldenstrom's macroglobulinemia. J Immunother. 1991;2001: 272–9.

Statement 1

Rituximab should be avoided or withheld, or preemptive plasma exchange should be performed in patients with high IgM levels due to risk of IgM flare.

Referenzen

7. Treon SP, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. Ann Oncol. 2004;15:1481–3.

Empfehlung 2 (Empfehlungsgrad 1B)

Chemoimmunotherapy combinations with rituximab, cyclophosphamide, and dexamethasone, benda-R, or bortezomib, rituximab, and dexamethasone provide durable responses with tolerable toxicity and are recommended in most patients.

Referenzen

9. Kastritis E, et al. Dexamethasone, rituximab, and cyclophosphamide as primary treatment of Waldenstrom macroglobulinemia: final analysis of a phase 2 study. Blood. 2015;126:1392–4.

Empfehlung 3 (Empfehlungsgrad 1B)

For high-risk patients or patients with hyperviscosity where rapid control of the disease is required bortezomib, nucleoside analogues-based regimens or bendamustin-based regimens should be preferred, while bortezomib should be avoided in patients with paraprotein-related neuropathy.

Referenzen

13. Rummel MJ, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381:1203–10.
15. Dimopoulos MA, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, lowdose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood. 2013;122:3276–82.

Empfehlung 4 (Empfehlungsgrad 1A)

For elderly patients, DRC or oral fludarabine should be treatments of choice.

Empfehlung 5 (Empfehlungsgrad 1A und 1B)

Ibrutinib represents an effective option for both treatment-naive and relapsing patients (1B) but is not recommended for patients with MYD88WT disease (1A).

Empfehlung 6 (Empfehlungsgrad 1B)

In the relapsed/refractory setting and in patients intolerant to rituximab ofatumumab can be considered.

Referenzen

8. Castillo JJ, et al. Rituximab intolerance in patients with Waldenstrom macroglobulinaemia. Br J Haematol. 2016;174:645–8.

Empfehlung 7 (Empfehlungsgrad 1B)

ASCT remains an option for high-risk patients, however the data available are very limited.

Referenzen

18. Kyriakou C, et al. Autologous stem cell transplantation (ASCT) for the treatment of patients with Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL). A risk factor analysis by the European Society for Blood and Marrow Transplantation (EBMT) Lymphoma Working Party [abstract]. Blood . 2014;124:678. Abstract

Empfehlung 8 (Empfehlungsgrad 1B)

Everolimus should be considered only for non-responders after multiple lines of therapy.

Statement 2

Treatment with any of the available therapeutic agents listed for untreated patients can be considered for previously treated patients requiring therapy.

Referenzen
14. Treon SP, et al. Bendamustine therapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2011;11:133–5.

Empfehlung 9 (Empfehlungsgrad 1C)

IMiDs and allogeneic SCT should be used only in the context of clinical trials.

Referenzen
19. Fouquet G, et al. Lenalidomide is safe and active in Waldenstrom macroglobulinemia. Am J Hematol. 2015;90:1055–9.
20. Treon SP, et al. Phase I study of pomalidomide, dexamethasone, rituximab (PDR) in patients with Waldenstrom's macroglobulinemia [abstract]. Proceedings of the 12th International Conference on Malignant Lymphoma. 19–22 June 2013. Lugano, Switzerland. Abstract 536.

Statement 3

Enrollment in clinical trials is highly recommended for patients with WM.

Weitere Referenzen
10. Treon SP, et al. Long-term outcomes to fludarabine and rituximab in Waldenstrom macroglobulinemia. Blood. 2009;113:3673–8.
11. Tedeschi A, et al. Fludarabine, cyclophosphamide, and rituximab in salvage therapy of Waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2013;13:231–4.
12. Souchet L, et al. Efficacy and long-term toxicity of the rituximab-fludarabine-cyclophosphamide combination therapy in Waldenstrom's macroglobulinemia. Am J Hematol. 2016;91:782–6.
16. Treon SP, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenstrom's macroglobulinemia. Blood. 2014;124:503–10.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Care Excellence (NICE), 2017 [5].

Ibrutinib for treating Waldenstrom’s macroglobulinaemia Technology appraisal guidance (TA 491)

1 Recommendations

1.1 Ibrutinib is recommended for use in the Cancer Drugs Fund as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.

1.2 This guidance is not intended to affect the position of patients whose treatment with ibrutinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

Summary of appraisal committee's key conclusions

Current praxis

Clinical need of patients, including the availability of alternative treatments: The committee concluded that there is no standard of care for treating Waldenstrom's macroglobulinaemia and that targeted therapy is highly valued by patients and addresses a significant unmet need.

Evidence for clinical effectiveness

Availability, nature and quality of evidence: The committee understood that the study PCYC-1118E was generally well reported but there were a number of potential biases because this was an open-label single arm study without a control group.

The committee understood that no clinical trial evidence had been presented for Waldenstrom's macroglobulinaemia in adults who have not had prior therapy and for whom chemo-immunotherapy is unsuitable. The committee appreciated that patients who have not had prior therapy and for whom chemo-immunotherapy is unsuitable have a particularly high unmet clinical need and it considered that the current lack of trial data for this group of patients was a limitation of the evidence base.

The committee was aware that the company had presented an indirect comparison of ibrutinib against existing treatments for Waldenstrom's macroglobulinaemia. This used the results from a Europe-wide chart review study; a retrospective observational study that generated data on epidemiology, treatment and efficacy outcomes for treatment-naive and relapsed Waldenstrom's macroglobulinaemia patients over 10 years.

Uncertainties generated by the evidence: The committee concluded that the longer term effects of ibrutinib on progression and survival are uncertain because no data is available.

The committee was aware that the company's indirect comparison suggested a substantial reduction in the risk of disease progression with ibrutinib compared with existing Waldenstrom's macroglobulinaemia therapies but that the ERG had a number of concerns with the company's approach. It accepted, based on the results of the indirect comparison and the testimonies from patients and clinical experts, that ibrutinib appears to be more clinically effective than existing treatments but there is considerable uncertainty about the size of the long-term benefit because of limitations in the data available.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews am 22.01.2019

#	Suchfrage
1	MeSH descriptor: [Waldenstrom Macroglobulinemia] explode all trees
2	(waldenstrom* OR waldenstroem* OR waldenström* OR primary):ti,ab,kw (Word variations have been searched)
3	(macroglobulinemia* OR macroglobulinaemia* OR macro-globulinemia* OR macro-globulinaemia*):ti,ab,kw (Word variations have been searched)
4	#2 AND #3
5	(lymphoplasmacytic OR lymphoplasmocytic OR lymphoplasmacytoid OR lymphoplasmocytoid OR lympho-plasmacytic OR lympho-plasmocytic OR lympho-plasmacytoid OR lympho-plasmocytoid OR lpl):ti,ab,kw (Word variations have been searched)
6	((plasmacytoid OR plasmocytoid) AND lymphocytic):ti,ab,kw (Word variations have been searched)
7	#5 OR #6
8	(lymphom*):ti,ab,kw (Word variations have been searched)
9	#7 AND #8
10	#1 OR #4 OR #9
11	MeSH descriptor: [Lymphoma, Non-Hodgkin] this term only
12	MeSH descriptor: [Lymphoma, B-Cell] this term only
13	((nonhodgkin* OR non-hodgkin* OR (non next hodgkin*) OR indolent OR b-cell) AND lymphom*):ti,ab,kw (Word variations have been searched)
14	#10 OR #11 OR #12 OR #13
15	#14 with Cochrane Library publication date from Jan 2014 to Jan 2019, in Cochrane Reviews and Cochrane Protocols

Systematic Reviews in Medline (PubMed) am 22.01.2019

#	Suchfrage
1	waldenstrom macroglobulinemia[MeSH Terms]
2	(waldenstrom*[Title/Abstract] OR waldenstroem*[Title/Abstract] OR primary[Title/Abstract])
3	(macroglobulinemia*[Title/Abstract] OR macroglobulinaemia*[Title/Abstract] OR macro-globulinemia*[Title/Abstract] OR macro-globulinaemia*[Title/Abstract])
4	(#2 AND #3)
5	(lymphoplasmacytic[Title/Abstract] OR lymphoplasmocytic[Title/Abstract] OR lymphoplasmacytoid[Title/Abstract] OR lymphoplasmocytoid[Title/Abstract] OR lympho-plasmacytic[Title/Abstract] OR lympho-plasmocytic[Title/Abstract] OR lympho-plasmacytoid[Title/Abstract] OR lympho-plasmocytoid[Title/Abstract] OR lpl[Title/Abstract])
6	((plasmacytoid[Title/Abstract] OR plasmocytoid[Title/Abstract])) AND lymphocytic[Title/Abstract]
7	(#5 OR #6)
8	lymphom*[Title/Abstract]
9	(#7 AND #8)
10	(#1 OR #4 OR #9)
11	(#10) AND ((Meta-Analysis[ptyp] 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 systematic 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 (systematic review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
12	(#11) AND ("2014/01/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 22.01.2019

#	**Suchfrage**
1	waldenstrom macroglobulinemia[MeSH Terms]
2	(waldenstrom*[Title/Abstract] OR waldenstroem*[Title/Abstract] OR primary[Title/Abstract])
3	(macroglobulinemia*[Title/Abstract] OR macroglobulinaemia*[Title/Abstract] OR macro-globulinemia*[Title/Abstract] OR macro-globulinaemia*[Title/Abstract])
4	(#2 AND #3)
5	(lymphoplasmacytic[Title/Abstract] OR lymphoplasmocytic[Title/Abstract] OR lymphoplasmacytoid[Title/Abstract] OR lymphoplasmocytoid[Title/Abstract] OR lympho-plasmacytic[Title/Abstract] OR lympho-plasmocytic[Title/Abstract] OR lympho-plasmacytoid[Title/Abstract] OR lympho-plasmocytoid[Title/Abstract] OR lpl[Title/Abstract])
6	((plasmacytoid[Title/Abstract] OR plasmocytoid[Title/Abstract])) AND lymphocytic[Title/Abstract]
7	(#5 OR #6)
8	lymphom*[Title/Abstract]
9	(#7 AND #8)
10	(#1 OR #4 OR #9)

11	"Lymphoma, Non-Hodgkin"[Mesh:NoExp]
12	"Lymphoma, B-Cell"[Mesh:NoExp]
13	((nonhodgkin*[Title/Abstract] OR non-hodgkin*[Title/Abstract] OR indolent[Title/Abstract] OR b-cell[Title/Abstract])) AND lymphom*[Title/Abstract]
14	(#10 OR #11 OR #12 OR #13)
15	(#14) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR guideline*[Title] OR recommendation*[ti])
16	(#15) AND ("2014/01/01"[PDAT] : "3000"[PDAT])
17	(#16) NOT retracted publication[ptyp]

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