Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2022-B-224-z Lisocabtagen maraleucel

Stand: September 2022

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

Lisocabtagen maraleucel

[zur Behandlung des r/r DLBCL, PMBCL und FL3B; ≥ 2 Linien einer systemischen Therapie]

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.	• Stammzelltransplantation • Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Tafasitamab (Beschluss vom 3. März 2022) • Obinutuzumab (Beschluss vom 4. November 2021) • Duvelisib (Beschluss vom 21. Juli 2021) • Tisagenlecleucel (Beschluss vom 17. September 2020) • Polatuzumab Vedotin (Beschluss vom 20. August 2020) • Axicabtagen-Ciloleucel (Beschluss vom 2. Mai 2019) • Idelalisib (Beschluss vom 19. März 2015) • Pixantron (Beschluss vom 16.Mai 2013) Richtlinie Methoden Krankenhausbehandlung, Stand 17. Februar 2022: - § 4 - Ausgeschlossene Methoden: Allogene Stammzelltransplantation bei erwachsenen Patienten mit aggressiven B-Non-Hodgkin-Lymphomen, die noch nicht mit autologer Stammzelltransplantation behandelt wurden - Anlage I - Methoden, die für die Versorgung im Krankenhaus erforderlich sind: Allogene Stammzelltransplantation bei erwachsenen Patienten mit aggressiven B-Non-Hodgkin-Lymphomen, die nach autologer Stammzelltransplantation rezidivieren und nach Salvage-Therapie ein Ansprechen mindestens im Sinne einer stabilen Erkrankung erreichen.
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:	
Lisocabtagen maraleucel N.N. N.N.	<u>Zu bewertendes Anwendungsgebiet:</u> Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL), primär mediastinalen großzelligen B-Zell-Lymphoms (PMBCL) und follikulären Lymphoms Grad 3B (FL3B) bei erwachsenen Patienten nach zwei oder mehr Linien einer systemischen Therapie.
Antineoplastische Mittel	
Bleomycin L01DC01 generisch	Non-Hodgkin-Lymphome von intermediärem oder hohem Malignitätsgrad im Erwachsenenalter. Bleomycinsulfat wird bei diesen Erkrankungen üblicherweise in Kombination mit anderen Zytostatika verwendet.
Cyclophosphamid L01AA01 generisch	Cyclophosphamid 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)
Cytarabin L01BC01 generisch	Cytarabin wird in Kombination mit anderen Zytostatika in konventionellen Dosen eingesetzt zur: - Behandlung von Non-Hodgkin-Lymphomen von intermediärem und hohem Malignitätsgrad im Erwachsenenalter Cytarabin wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: - - refraktären Non-Hodgkin-Lymphomen
Doxorubicin L01DB01 generisch	hochmaligne Non-Hodgkin-Lymphome
Etoposid L01CB01 generisch	Etoposid ist in Kombination mit anderen zugelassenen Chemotherapeutika angezeigt zur Behandlung von Non-Hodgkin-Lymphomen bei erwachsenen und pädiatrischen Patienten.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ifosfamid L01AA06 generisch	Non-Hodgkin-Lymphome: Zur Kombinationschemotherapie bei Patienten mit hochmalignen Non-Hodgkin-Lymphomen, welche nicht oder nur unzureichend auf die Initialtherapie ansprechen. Zur Kombinationstherapie von Patienten mit rezidiven Tumoren.
Melphalan L01AA03 Phelinun®	Hochdosiertes PHELINUN, das als Monotherapie oder in Kombination mit anderen zytotoxischen Arzneimitteln und/oder einer Ganzkörperbestrahlung angewendet wird, wird angewendet bei Behandlung von: - […] malignen Lymphomen (Hodgkin-Lymphom, Non-Hodgkin-Lymphom),
Methotrexat L01BA01 generisch	Non-Hodgkin-Lymphome: - im Erwachsenenalter: Zur Behandlung von Non-Hodgkin-Lymphomen von intermediärem oder hohem Malignitätsgrad in Kombination mit anderen zytostatischen Arzneimitteln
Mitoxantron L01DB07 generisch	Mitoxantron ist indiziert zur Behandlung des Non-Hodgkin-Lymphoms.
Pixantron L01DB11 Pixuvri®	Die Monotherapie mit Pixuvri ist indiziert zur Behandlung von erwachsenen Patienten mit mehrfach rezidivierten oder therapierefraktären aggressiven Non-Hodgkin-B-Zell-Lymphomen (NHL). Der Nutzen der Pixantron-Behandlung bei Anwendung als Fünft- und Mehrlinientherapie bei Patienten, die refraktär gegen die vorausgegangene Therapie waren, ist nicht erwiesen.
Trofosfamid L01AA07 generisch	Dieses Arzneimittel ist ein Zytostatikum. Trofosfamid wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet.
Vinblastin L01CA01 generisch	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 generisch	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen
Vindesin L01CA03 generisch	Kombinationschemotherapie: aggressives Non-Hodgkin-Lymphom (Stadium I oder II)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Glucocorticoide	
Dexamethason H02AB02 generisch	Onkologie: Palliativtherapie maligner Tumoren Prophylaxe und Therapie von postoperativem oder Zystostatika-induzierten Erbrechen im Rahmen antiemetischer Schmerz
Methylprednisolon H02AB04 Methylprednisolon JENAPHARM®	Blutkrankheiten/Tumorerkrankungen - Autoimmunhämolytische Anämie - Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen, Anwendung im Rahmen antiemetischer Schemata […]“
Prednisolon H02AB06 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Prednison H02AB07 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Antikörper-Wirkstoff-Konjugate	
Polatuzumab Vedotin L01XC37 Polivy®	Polivy in Kombination mit Bendamustin und Rituximab wird angewendet zur Behandlung erwachsener Patienten mit rezidivierendem oder refraktärem diffusem großzelligem B-Zell-Lymphom (DLBCL), die nicht für eine hämatopoetische Stammzelltransplantation in Frage kommen.
Monoklonale Antikörper	
Rituximab L01XC02 MabThera®	Non-Hodgkin-Lymphom (NHL): - MabThera ist für die Behandlung von Patienten mit CD20-positivem, diffusem großzelligen B-Zell-Non-Hodgkin-Lymphom in Kombination mit einer CHOP(Cyclophosphamid, Doxorubicin, Vincristin, Prednisolon)-Chemotherapie angezeigt.
Tafasitamab L01FX12 Minjuvi	MINJUVI wird angewendet in Kombination mit Lenalidomid gefolgt von einer MINJUVI-Monotherapie für die Behandlung bei erwachsenen Patienten mit rezidiviertem oder refraktärem diffusem großzelligem B-Zell-Lymphom (diffuse large B-cell lymphoma, DLBCL), für die eine autologe Stammzelltransplantation (ASZT) nicht infrage kommt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
CAR-T-Zellen	
Axicabtagen-Ciloleucel L01XX70 Yescarta®	YESCARTA wird angewendet zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem diffus großzelligem B-Zell Lymphom (DLBCL) und primär mediastinalem großzelligem B-Zell-Lymphom (PMBCL) nach zwei oder mehr systemischen Therapien.
Tisagenlecleucel L01XX91 Kymriah®	Kymriah wird angewendet zur Behandlung von: erwachsenen Patienten mit rezidiviertem oder refraktärem diffus großzelligen B-Zell-Lymphom (DLBCL) nach zwei oder mehr Linien einer systemischen Therapie. erwachsenen Patienten mit rezidiviertem oder refraktärem follikulären Lymphom (FL) nach zwei oder mehr Linien einer systemischen Therapie.
Ausschließlich für das FL zugelassene Arzneimittel	
Duvelisib[1] L01EM04 Copiktra®	Erwachsene Patienten mit follikulärem Lymphom (FL), das gegenüber mindestens zwei vorherigen systemischen Therapien refraktär ist.
Ibritumomab-Tiuxetan V10XX02 Zevalin®	[90Y]-radiomarkiertes Zevalin ist indiziert zur Behandlung von erwachsenen Patienten mit einem nach einer Behandlung mit Rituximab rezidivierenden oder refraktären CD20-positiven follikulären Non-Hodgkin-Lymphom (NHL) vom B-Zell-Typ.
Idelalisib L01XX47 Zydelig®	Zydelig wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär nach zwei vorausgegangenen Therapielinien ist, angewendet.
Interferon alfa-2a L03AB05 Roferon®-A	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: - Follikuläres Non-Hodgkin-Lymphom.
Interferon alfa-2b L03AB05 IntronA®	Follikuläre Lymphome: Therapie follikulärer Lymphome mit großer Tumormasse zusätzlich zu geeigneter Kombinations-Chemotherapie zur Induktion wie CHOP-ähnliche Behandlungsschemata.

[1] Derzeit in Deutschland nicht im Handel.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Mosunetuzumab L01XC Lunsumio®	Lunsumio als Monotherapie ist angezeigt für die Behandlung von erwachsenen Patienten mit rezidivierendem oder refraktärem follikulärem Lymphom (FL), die bereits mindestens zwei vorherige systemische Behandlungen erhalten haben.
Obinutuzumab L01XC15 Gazyvaro®	Gazyvaro in Kombination mit Bendamustin, gefolgt von einer Gazyvaro Erhaltungstherapie, wird angewendet bei Patienten mit FL, die auf eine Behandlung mit Rituximab oder einem Rituximab-haltigen Regime nicht angesprochen haben oder während bzw. bis zu 6 Monate nach der Behandlung progredient wurden.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2022-B-224-z (Lisocabtagen maraleucel)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. Mai 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event/s
(A)SCT	(Autologous) Stem cell transplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BEAM	BCNU + etoposide + cytarabine + melphalan
BMT	Bone marrow transplantation
CAR	Chimeric antigen receptor
CEPP	cyclophosphamide + etoposide + procarbazine + prednisone
CLL	Chronic lymphocytic leukemia
CMA	Canadian Medical Association
CMR	Complete metabolic response
CNS	Central nervous system
CR	Complete remission
CRR	Complete Response Rate
CRS	Cytocine release syndrome
CT	Computertomographie
CVP	cyclophosphamide + cincristine + prednisone
DA-EPOCH-R	Dose-adjusted etoposide + vincristine + doxorubicin + cyclophosphamide + prednisone + rituximab
DHL	Double-hit lymphoma
DLBCL	Diffuses großzelliges B-Zell-Lymphom
ECOG	Eastern Cooperative Oncology Group
ECRI	ECRI Guidelines Trust
EFS	Event free survival
FISH	Fluorescence *in situ* hybridisation
FL(3B)	Folikuläres Lymphom (Grad 3)
FND	fludarabine + mitoxantrone + dexamethasone
G-BA	Gemeinsamer Bundesausschuss
GC(B)	Germinal centre (B-cell)
G-CSF	Granulozyten-Kolonie.stimulierener Faktor
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HD(C)T	High-dose chemotherapy

HDMTX	High-dose methotrexate
HR	Hazard Ratio
IFRT	Involved field radiotherapy
IPI	International Prognostic Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LDH	Lactate dehydrogenase
LoE	Level of Evidence
MEP	Mitoxantrone + etoposide + prednisone
MYC	MYC-Gen
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin-Lymphom
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
PCLBCL (NOS)	Primary cutaneous diffuse large B-cell lymphoma (not otherwise specified)
PEPC	Phosphoenolpyruvatcarboxylase
PET	Positronenemissionstomographie
PFS	Progression free survival
PMBCL	Primär mediastinales großzelliges B-Zell-Lymphom
PR	Partial Remission
PRISMA-S	Preferred Reporting Items for Systematic Reviews and Metaanalyses literature search extension
PRESS	Peer Review of Electronic Search Strategies
r/r	relapsed / refractory
R-BEAM	rituximab + BCNU + etoposide + cytarabine + melphalan
R-BuMel	rituximab + busulfan + melphalan hydrochloride
RCHOP	rituximab + cyclophosphamide + doxorubicin + cincristine + perdisone
R-COSOX-M/ IVAC	rituximab + cyclophosphamide + cincristine + doxorubicin + methotrexate / rituximab + ifosfamide + etoposide + cytarabine
RCT	Randomisierte kontrollierte Studie/n
R-DHAP	rituximab + cisplatin + cytarabine + dexamethasone
R-DICEP	rituximab + dose-itensive cyclophosphamide + etoposide
R-GDP	rituximab + cisplatin + gemcitabine + dexamethasone
R-GemOx	rituximab + gemcitabine + oxaliplatin
R-ICE	rituximab + ifosfamide + carboplatin + etoposide

R-MelTIBI	rituximab + melphalan + total body irradiation
RR	Relatives Risiko
RT	Radiation therapy
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database

1 Indikation

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL), primär mediastinalen großzelligen B-Zell-Lymphoms (PMBCL) und follikulären Lymphoms Grad 3B (FL3B)

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 zu den Indikationen *diffus großzelliges B-Zell-Lymphom (DLBCL), primär mediastinales großzelliges B-Zell-Lymphom (PMBCL), follikuläres Lymphom Grad 3B (FL3B) und T-Zell/Histiozyten-reiches großzelliges B-Zell-Lymphom (THRBCL)* 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 Leitlinien-organisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 22.10.2021 durchgeführt, die folgende am 17.05.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 603 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 10 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Ernst M et al., 2021 [3].

Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma.

Fragestellung

To assess the benefits and harms of chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory (r/r) DLBCL.

Methodik

Population:

- individuals with a confirmed diagnosis of DLBC

Intervention/Komparator:

- CAR T-cell therapy versus control treatment, for example, standard treatment (e.g. chemotherapy, high-dose chemotherapy, monoclonal antibodies, autologous stem-cell transplantation and allogenic stem-cell transplantation). Co-interventions would have been required to be comparable between intervention groups.
- CAR T-cell therapy combined with other drugs versus standard treatment.

Endpunkte:

- Overall survival, Quality of life, Treatment-related mortality, AEs, PFS, Response to treatment

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE and EMBASE until September 11th, 2020.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 eligible uncontrolled studies evaluating a single or multiple arms of CAR T-cell therapies.
- 38 ongoing studies, including three RCTs.
- Ten studies are awaiting classification due to completion with no retrievable results data or insufficient data to justify inclusion.

Charakteristika der Population:

- The mean number of participants enrolled, treated with CAR T-cell therapy and evaluated in the included studies were 79 (range 12 to 344; data unavailable for two studies), 61 (range 12 to 294; data unavailable for one study) and 52 (range 11 to 256), respectively.

- Most studies included people with r/r DLBCL among people with other haematological B-cell malignancies. Participants had received at least a median of three prior treatment lines (data unavailable for four studies), 5% to 50% had undergone ASCT (data unavailable for five studies) and, except for two studies, 3% to 18% had undergone allogenic stem-cell transplantation (data unavailable for eight studies).

Qualität der Studien:

- The overall risk of bias was high for all studies, in particular, due to incomplete follow-up and the absence of blinding. None of the included studies had a control group so that no adequate comparative effect measures could be calculated. The duration of follow-up varied substantially between studies, in particular, for harms. Our certainty in the evidence is very low for all outcomes.

Studienergebnisse:

- Overall survival was reported by eight studies (567 participants). Four studies reported survival rates at 12 months which ranged between 48% and 59%, and one study reported an overall survival rate of 50.5% at 24 months. The evidence is very uncertain about the effect of CAR T-cell therapy on overall survival.
- Two studies including 294 participants at baseline and 59 participants at the longest follow-up (12 months or 18 months) described improvements of quality of life measured with the EuroQol 5-Dimension 5-Level visual analogue scale (EQ-5D-5L VAS) or Function Assessment of Cancer Therapy-Lymphoma (FACT-Lym). The evidence is very uncertain about the effect of CAR T-cell therapy on quality of life.
- None of the studies reported treatment-related mortality.
- Five studies (550 participants) reported the occurrence of adverse events among participants, ranging between 99% and 100% for any grade adverse events and 68% to 98% for adverse events grade ≥ 3. In three studies (253 participants), 56% to 68% of participants experienced serious adverse events, while in one study (28 participants), no serious adverse events occurred. CAR T-cell therapy may increase the risk of adverse events and serious adverse events but the evidence is very uncertain about the exact risk.
- The occurrence of cytokine release syndrome (CRS) was reported in 11 studies (675 participants) under use of various grading criteria. Five studies reported between 42% and 100% of participants experiencing CRS according to criteria described in Lee 2014. CAR T-cell therapy may increase the risk of CRS but the evidence is very uncertain about the exact risk.
- Nine studies (575 participants) reported results on progression-free survival, disease-free survival or relapse-free survival. Twelve-month progression-free survival rates were reported by four studies and ranged between 44% and 75%. In one study, relapse-free survival remained at a rate of 64% at both 12 and 18 months. The evidence is very uncertain about the effect of CAR T-cell therapy on progression free survival.
- Thirteen studies (620 participants) provided data on complete response rates. At six months, three studies reported complete response rates between 40% and 45%. The evidence is very uncertain about the effect of CAR T-cell therapy on complete response rates.

Anmerkung/Fazit der Autoren

The available evidence on the benefits and harms of CAR T-cell therapy for people with r/r DLBCL is limited, mainly because of the absence of comparative clinical trials. The results

we present should be regarded in light of this limitation and conclusions should be drawn very carefully. Due to the uncertainty in the current evidence, a large number of ongoing investigations and a risk of substantial and potentially life-threatening complications requiring supplementary treatment, it is critical to continue evaluating the evidence on this new therapy.

3.2 Systematische Reviews

Ying Z et al., 2022 [10].

Effectiveness and Safety of Anti-CD19 Chimeric Antigen Receptor-T Cell Immunotherapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma: A Systematic Review and Meta-Analysis.

Fragestellung

To investigate the effectiveness and safety of using chimeric antigen receptor (CAR) T cell therapies targeting CD19 in patients with diffuse large B-cell lymphoma (DLBCL).

Methodik

Population:

- patients (aged ≥18 years old) with measurable, histologically confirmed r/r DLBCL, including the subtypes based on the 2008 WHO Classification, and who failed to at least two lines of systemic treatment

Intervention/Komparator:

- anti-CD19 CAR-T cell immunotherapy

Endpunkte:

- clinical response outcomes, survival outcomes, and safety analyses

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library were searched for reports published from database inception up to July 2021

Qualitätsbewertung der Studien:

- Methodological Index for Non-Randomized Studies (MINORS) tool for clinical trials and the NewcastleOttawa Scale (NOS) tool for observational studies

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty-seven studies (1,687 patients)

Charakteristika der Population:

- Sixteen studies were from the United States, five from Europe, four from China, and two were multicenter studies performed in multiple countries. Eight studies reported data about tisagenlecleucel, fourteen about axicabtagene ciloleucel, one about relmacabtagene autoleucel, two about lisocabtagene maraleucel, and four about non-commercial preparations

Qualität der Studien:

- Among the observational studies, two scored five stars on the NOS, one scored six stars, one scored seven stars, and one scored eight stars. The clinical trials scored 19–24 points on the MINORS.

Studienergebnisse:

- The pooled 12-months overall survival (OS) rate was 63% (95%CI: 56–70%).
- The pooled best overall response (BOR) was 74.0% (95%CI: 67–79%), with a best complete response (BCR) of 48% (95%CI: 42–54%) and a 3-months CR rate (CRR) of 41% (95%CI: 35–47%).
- The subgroup analyses by costimulatory domain suggested statistically significant differences in BOR and BCR, whereas not in the 12-months OS rate and 3-months CRR.
- Among the patients evaluable for safety, 78% (95%CI: 68–87%), 6% (95%CI: 3–10%), 41% (95%CI: 31–52%), and 16% (95%CI: 10–24%) experienced cytokine release syndrome (CRS), severe CRS, neurotoxicity, and severe neurotoxicity, respectively.
- Compared with the CD28 costimulatory domain, the 41BB-based products showed a better safety profile on any-grade CRS ($p < 0.01$), severe CRS ($p = 0.04$), any-grade neurotoxicity ($p < 0.01$), and severe neurotoxicity ($p < 0.01$).

Anmerkung/Fazit der Autoren

The present meta-analysis demonstrated excellent effectiveness and manageable safety profile ofCD19-targeting CAR-T cells in patients with r/r DLBCL. The subgroup analyses suggested that 4-1BB- and CD28-based CAR-T cells have similar 12-months OS rates and 3months CRR in patients with r/r DLBCL, but 4-1BB-based CAR-T cells have a better safety profile. Among the 4-1BB products, relmacabtagene autoleucel might have better efficacy than tisagenlecleucel. However, as a newly approved product, relmacabtagene autoleucel lacks real-world data to confirm its long-term clinical benefits. Furthermore, CAR-T cell manufacturing is complex, and discrepancies exist between products using the same costimulatory domain. We suggest future studies to report detailed information about the CAR-T constructs.

Li J et al., 2021 [7].

Efficacy and Safety of Lenalidomide Monotherapy for Relapsed/Refractory Diffuse Large B Cell Lymphoma: Systematic Review and Meta-Analysis.

Fragestellung

to assess the efficacy and safety of lenalidomide monotherapy in these patients.

Methodik

Population:

- DLBCL patients with R/R status

Intervention:

- lenalidomide monotherapy

Komparator:

- siehe Ergebnisteil

Endpunkte:

- response rates, adverse events (AEs), overall survival (OS), and progression-free survival (PFS)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and the Cochrane Library databases were searched for publications up to April 7, 2021

Qualitätsbewertung der Studien:

- ROBINS-I tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 publications from 10 studies from that were published from 2008 to 2020

Charakteristika der Population:

- Five of these studies were prospective one-arm studies, four were retrospective analyses, and one was a randomized controlled trial. The sample size ranged from 15 to 153 patients, and the median patient age ranged from 51 to 79 years old.

Qualität der Studien:

- The included studies had variable quality. Moreover, because these data were from one-arm interventions, each study had a high risk of confounding.
- Six studies were classified as having problems with selection bias.
- The one RCT, in which our extracted data were targeted as a one-arm treatment, also had a high risk of confounding.

Studienergebnisse:

- The cumulative objective response rate (ORR) for lenalidomide monotherapy was 0.33 (95% CI: 0.26, 0.40), and the ORR was better in patients with the non-GCB phenotype (0.50; 95% CI: 0.26, 0.74) than the GCB phenotype (0.06; 95% CI: 0.03, 0.11).
- The major serious treatment-related AEs were neutropenia, thrombocytopenia, respiratory disorders, anemia, and diarrhea.
- The median PFS ranged from 2.6 to 34 months and the median OS ranged from 7.8 to 37 months.

Fazit der Autoren

The results of the present study suggest that lenalidomide monotherapy was active for DLBCL patients with R/R status and leads to AEs that are mostly manageable. The non-GCB subgroup of these patients had greater tumor responsiveness than the GCB subgroup.

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2020 [6] & [5].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft,, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)

Diagnostik, Therapie und Nachsorge für Patienten mit einem follikulären Lymphom.

Zielsetzung/Fragestellung

Das primäre Ziel dieser S3-Leitlinie ist es, die Diagnostik, Therapie und Nachsorge von Patienten mit einem follikulären Lymphom (FL) zu standardisieren und zu optimieren, um sowohl bei der Ersterkrankung als auch beim Rezidiv ein individuell adaptiertes qualitätsgesichertes Therapiekonzept zu gewährleisten.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Gültig bis 21.06.2025

Recherche/Suchzeitraum:

- von 1994 bis 2017

LoE/GoR

- GRADE

Tabelle 4: Vertrauen in den Evidenzkörper gemäß GRADE

Qualität der Evidenz	Beschreibung	Symbol
Hohe Qualität	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderate Qualität	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringe Qualität	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringe Qualität	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

Tabelle 5: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 6: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Empfehlungen

Therapie des Rezidivs

11.1.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Bei Patienten mit einem behandlungsbedürftigen systemischen Rezidiv oder Progress ***sollte*** eine systemische Therapie durchgeführt werden.
GRADE ⊕⊕⊕⊖ moderate ⊕⊕⊕⊕ high ⊕⊕⊕⊖ moderate ⊕⊕⊖⊖ low	van Oers 2006 [287], Radford 2013 [288], Sehn 2016 [289] Gesamtüberleben Pogressionsfreies Überleben Lebensqualität Sicherheit
	Starker Konsens

11.2.	Konsensbasierte Empfehlung
EK	Bei einem Rezidiv oder Progress nach mehr als 2 Jahren nach einer Chemoimmuntherapie ***sollte*** bei entsprechender Therapieindikation erneut eine Chemoimmuntherapie eingesetzt werden. *CAVE: Kumulative Antrazyklin-Toxizität beachten. Erhöhte Rate an Sekundärneoplasien unter Fludarabin beachten.*
	Starker Konsens

11.3.	Konsensbasierte Empfehlung
EK	Bei einem Rezidiv oder Progress nach mehr als 2 Jahren nach einer Chemoimmuntherapie ***kann*** bei entsprechender Therapieindikation die gleiche Chemoimmuntherapie wieder eingesetzt werden. *CAVE: Kumulative Antrazyklin-Toxizität beachten. Erhöhte Rate an Sekundärneoplasien unter Fludarabin beachten.*
	Starker Konsens

11.4.	Konsensbasierte Empfehlung
EK	Bei einem Rezidiv oder Progress nach weniger als 2 Jahren nach Beginn einer Chemoimmuntherapie ***sollte,*** sofern verfügbar, die Behandlung im Rahmen klinischer Studien angeboten werden.
	Starker Konsens

11.5.	Konsensbasierte Empfehlung
EK	Bei einem Rezidiv oder Progress nach weniger als 2 Jahren nach Beginn einer Chemoimmuntherapie ***sollten*** bei geeigneten Patienten andere Therapieverfahren (z.B. eine Hochdosistherapie mit nachfolgender autologer Stammzelltransplantation) eingesetzt werden.
	Starker Konsens

11.6.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Bei einem Rezidiv während oder innerhalb von 6 Monaten nach einer Rituximabtherapie ***sollte*** bei Indikation zur erneuten Chemoimmuntherapie Obinutuzumab als Antikörper in Betracht gezogen werden. *CAVE: Zulassung von Obinutuzumab im Rezidiv nur mit Bendamustin*
GRADE ⊕⊕⊕⊕ high ⊕⊕⊕⊕ high ⊕⊕⊕⊖ moderate ⊕⊕⊕⊖ moderate	Sehn 2016 [289] Gesamtüberleben Progressionsfreies Überleben Lebensqualität Sicherheit
	Konsens

11.7.	Konsensbasierte Empfehlung
EK	Eine Monotherapie mit Rituximab ***kann*** besonders bei älteren oder komorbiden Patienten, bei denen eine Chemotherapie nicht durchführbar ist, in der Rezidivtherapie eingesetzt werden.
	Starker Konsens

11.8.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Eine Radioimmuntherapie (Yttrium-90-Ibritumomab-Tiutexan) ***kann*** bei einer Knochenmarkinfiltration <20 % im Rezidiv eingesetzt werden, wenn Patienten nicht für eine Immunchemotherapie oder Chemotherapie geeignet sind.
GRADE Nicht berichtet ⊕⊕⊖⊖ low Nicht berichtet ⊕⊕⊖⊖ low	Witzig 2002 [299, 300] Gesamtüberleben Progressionsfreies Überleben Lebensqualität Sicherheit
	Starker Konsens

Neue Substanzen mit Zulassung beim follikulären Lymphom

11.2.1.1. Idelalisib

11.9.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Patienten ab dem zweiten Rezidiv oder Progress nach Chemo- und/oder Immuntherapie ***können*** eine Monotherapie mit Idelalisib erhalten, wenn die letzte Chemo und/oder Immuntherapie ungenügend angesprochen hat (Progress innerhalb von 6 Monaten)
GRADE ⊕⊕⊖⊖ low ⊕⊕⊖⊖ low Nicht berichtet ⊕⊖⊖⊖very low	Salles 2016 [302], Eyre 2018 [303], Gopal 2014 [281] Gesamtüberleben Progressionsfreies Überleben Lebensqualität Sicherheit
	Starker Konsens

Neue Substanzen ohne Zulassung, jedoch breiter Studienlage

11.2.2.1. Lenalidomid

11.10.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Eine Behandlung mit Rituximab und Lenalidomid ***kann*** vor allem bei Patienten erfolgen, die nach Chemoimmuntherapie refraktär oder nur kurz in Remission sind, und bei denen eine Therapie mit Idelalisib oder eine intensive Salvage-Therapie nicht möglich ist und bei denen kein experimenteller Ansatz in Studien zur Verfügung steht. *CAVE: Off-label use Lenalidomid*
GRADE ⊕⊕⊖⊖ low Nicht berichtet Nicht berichtet ⊕⊕⊕⊖ moderate	Leonard 2015 [305] Gesamtüberleben Progressionsfreies Überleben Lebensqualität Sicherheit
	Starker Konsens

11.2.2.2. Copanlisib, Duvelisib, Ibrutinib, Venetoclax und PD-1 / PD-L1Antikörper

11.11.	Konsensbasierte Empfehlung
EK	Copanlisib, Duvelisib, Ibrutinib, Venetoclax und PD-1 / PD-L1 interagierende Antikörper ***sollten nicht*** außerhalb von klinischen Studien angewendet werden.
Ibrutinib	Bartlett 2018 [309], Gopal 2018 [310]
⊕⊕⊖⊖ low	Gesamtüberleben
⊕⊕⊖⊖ low	Progressionsfreies Überleben
Nicht berichtet	Lebensqualität
⊕⊕⊖⊖ low	Sicherheit
PD-1/PD-L1-interagierende Antikörper	Lesokhin 2016 [311]
Nicht berichtet	Gesamtüberleben
⊕⊖⊖⊖ very low	Progressionsfreies Überleben
Nicht berichtet	Lebensqualität
Nicht berichtet	Sicherheit
	Starker Konsens

Follikuläre Lymphome Grad 3B

9.7.	Konsensbasierte Empfehlung
EK	Patienten mit einem follikulären Lymphom Grad 3B ***sollen*** wie de novo diffuse großzellige B Zell Lymphome (DLBCL) behandelt werden.
	Starker Konsens

National Institute for Health and Care Excellence, 2016 [9].

Non-Hodgkin's lymphoma: diagnosis and management

Zielsetzung

This guideline covers diagnosing and managing non-Hodgkin's lymphoma in people aged 16 years and over. It aims to improve care for people with non-Hodgkin's lymphoma by promoting the best tests for diagnosis and staging and the most effective treatments for 6 of the subtypes. Tests and treatments covered include excision biopsy, radiotherapy, immunochemotherapy and stem cell transplantation.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,

- Konsensfindung erwähnt, aber nicht detailliert beschrieben[1], externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards
- Web of Science [specifically Science Citation Index Expanded (SCI-Expanded) 1900 onwards and Social Sciences Citation Index (SSCI) 1900 onwards]

Subject specific databased used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1937 onwards
- PsycINFO 1806 onwards
- Allied and Complementary Medicine (AMED) 1985 onwards

[…] searches were updated and re-run 8 weeks before the guideline was submitted to NICE for stakeholder consultation. […] Any evidence published after this date was not included. For the purposes of updating this guideline, 1st September 2015 should be considered the starting point for searching for new evidence.

LoE

Tabelle 4: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GoR

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. […] Recommendations were based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence. […] Terms used within this guideline are:

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm (based on high quality evidence)

[1] In most cases the committee reaches decisions through a process of informal consensus, but sometimes formal voting procedures are used (siehe 'Developing NICE guidelines: the manual')

- 'Do not offer' – the intervention will not be of benefit for most patients (based on high quality evidence)
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients (based on poor quality evidence or no evidence). The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendations

Offer salvage therapy with multi-agent immunochemotherapy to people with relapsed or refractory diffuse large B-cell lymphoma who are fit enough to tolerate intensive therapy:

- Explain that this is primarily to obtain sufficient response to allow consolidation with autologous or allogeneic stem cell transplantation, but is also beneficial even if not followed by transplantation.
- Consider R-GDP immunochemotherapy, which is as effective as other commonly used salvage regimens and less toxic.

Offer consolidation with autologous stem cell transplantation to people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial response to chemotherapy) who are fit enough for transplantation.

Consider consolidation with allogeneic stem cell transplantation for people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial reponse to chemotherapy):

- that relapses after autologous stem cell transplantation or
- in whom stem cell harvesting is not possible.

Quality of the evidence

The quality of the evidence was moderate to very low using GRADE.

Evidence comparing transplantation to non-transplantation strategies was lacking. The randomised trials involving autologous transplantation compared different salvage chemotherapy regimens. Only non comparative studies were available for allogeneic transplantation. This limited the strength of the recommendation that the GC were able to make about allogeneic transplantation.

Trade-off between clinical benefits and harms

The GC considered that the recommendation to offer salvage therapy and consolidation with autologous transplantation would prolong overall survival. Evidence from trials comparing different salvage chemotherapies followed by autologous stem cell transplant indicated overall survival of around 40% and event free survival around 30%.

The use of high dose therapy with autologous transplantation however is associated with toxicity including late effects and in some cases treatment related mortality.

The GC considered that the increased overall survival outweighed the harms due to acute and late effects.

The recommendation to consider salvage therapy R-GDP instead of R-DHAP, has the potential to reduce treatment related toxicity without adversely affecting overall survival. This recommendation was informed by a randomised trial which indicated R-GDP was as

effective as R-DHAP with similar overall and event free survival, but with fewer serious adverse events (47% versus 60%).

Evidence about allogeneic stem cell transplant indicated overall survival of around 40% at five years with similar rates of acute and chronic graft versus host disease.

4.4.3.1 Clinical evidence

Evidence came from three randomised controlled trials, three retrospective cohort studies and four retrospective case series.

4.4.3.1.1 R-BEAM followed by ASCT versus B-BEAM followed by ASCT

Low quality evidence from one study of 224 patients reported that overall rate of grade 3-5 non-haematologic toxicities and grade 3-5 mucositis, but not other individual grade 3-5 non-haematologic toxicities, overall survival, progression-free survival, and treatment-related mortality were significantly lower in R-BEAM than B-BEAM (HRs not reported [BMT CTN 0401]).

4.4.3.1.2 R-ICE followed by ASCT versus R-DHAP followed by ASCT

One study (CORAL) with 477 patients provided moderate quality evidence that overall survival, progression-free survival, and event-free survival did not differ significantly between R-ICE and R-DHAP (HRs not reported).

4.4.3.1.3 (R-)GDP followed by ASCT versus (R-)DHAP followed by ASCT

One study with 619 patients (NCIC-CTG LY-12) provided low quality evidence that quality of life was significantly better or similar in (R-)GDP compared to (R-)DHAP and grade 3-4 nausea, febrile neutropenia and overall occurred significantly less in (R-)GDP than in (R-)DHAP, but the treatment groups did not differ in other individual grade 3-4 adverse events, overall survival, overall survival after transplantation, event-free survival, event-free survival after transplantation, overall response rate and rate of ASCT transplantation (HRs not reported),

4.4.3.1.4 R-ICE versus R-GDP as salvage chemotherapy

Low quality evidence from an indirect comparison of two randomised trials (CORAL and NCIC-CTG LY.12) suggested uncertainty about whether outcomes are better with R-GDP than with RICE.

4.4.3.1.5 R(if CD+)-ICE followed by ASCT (if < 66 years and response) versus R(if CD+)-DHAP followed by ASCT (if < 66 years and response) versus R(if CD+)-GDP followed by ASCT (if < 66 years and response)

Very low quality evidence from one study with 113 patients (Kusano et al, 2014) reported median second progression-free survival was longer in (R-)ICE than in two other two treatment groups combined and in (R-)ICE compared to (R-)DHAP alone, but not to (R-)GDP alone. There was significantly more grade 3-4 renal dysfunction with (R-)DHAP than in other two treatment groups, but the three treatment groups did not differ in overall or complete response, overall survival ((R-)ICE versus the other two treatment groups combined), median time from first progression to second progression or last follow up, and grade 3-4 haematological side effects (HRs not reported).

4.4.3.1.6 R-MICE versus R-DICEP

Oh et al (2015) provided very low quality evidence that median time to progression was significantly longer in R-MICE than R-DICEP (HR not reported; n = 38).

4.4.3.1.7 R-GemOx versus RICE

Very low quality evidence from one study with 65 patients (Zhang et al, 2011) suggest that neutrocytopenia and gastrointestinal tract reactions occured significantly more in RICE than R-GemOx (HR not reported).

4.4.3.1.8 Allogeneic transplantation

Very low quality evidence about outcomes following allogeneic transplantation came from 4 retrospective case series (Avivi et al, 2014; Rigacci et al, 2012; Sirvent et al, 2010 and van Kampen et al, 2011) including 807 patients. Overall survival at five years after allogeneic stem cell transplant (allo-SCT) ranged from 34% to 43% and five year progression free survival ranged from 30% to 37%. The rates of non-relapse mortality ranged from 28% to 38%, rates of acute graft-versus-host disease ranged from 32% to 51% and rates of chronic graft-versus-host disease ranged from 35% to 42%.

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Cwynarski K et al., 2019 [2].

British Society for Haematology (BSH)

The management of primary mediastinal B-cell lymphoma: a British Society for Haematology Good Practice Paper.

Zielsetzung

The BSH produces Good Practice Papers to recommend good practice in areas where there is a limited evidence base but for which a degree of consensus or uniformity is likely to be beneficial to patient care.

Methodik

Grundlage der Leitlinie

- Keine Beteiligung von Patientenvertretungen an der Leitlinienerstellung, lediglich zur externen Begutachtung vorgelegt2,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Angaben zur systematischen Auswahl fehlen, kritische Bewertung der Literatur im Rahmen der Bewertung der Vertrauenswürdigkeit der Evidenz mit GRADE, aber keine Details beschrieben,
- Verfahren zur Konsensfindung nicht erwähnt, externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Gültigkeit nicht erwähnt, Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

The PubMed database was searched for English language articles up to August 2018 […]. The references from relevant publications were searched and published guidelines by the European Society for Medical Oncology were noted.

LoE/GoR

GRADE nomenclature	
Strengh of recommendation	
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 uniformely 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

[2] The manuscript was reviewed by representatives from the Lymphoma Association; this organisation does not necessarily approve or endorse the contents.

	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, care series or just opinion.

Recommendations

Relapse or Refractory Disease

Consider radiotherapy if omitted from initial therapy with localized relapse (1B).

Patients should be offered a clinical trial wherever possible (1A).

The choice of salvage regimen should be the same as those used in the treatment of relapsed diffuse large B-cell lymphoma with consolidation HDT/autologous stem cell transplantation (ASCT) for response disease. Radiotherapy pre- or post-ASCT should be considered if previously omitted (2B).

Hintergrund

Patients in whom consolidation RT was omitted should be considered for RT if presenting with residual localized mediastinal disease that is fluoro-deoxyglucose (FDG)-avid on PET-CT and, if feasible, a biopsy should be performed to prove recurrent or residual disease.

There is a lack of data regarding the optimal 'salvage' chemotherapy regimen for relapsed PMBCL, in whom CMR has been achieved previously. Therefore, it appears reasonable that the approach to 'salvage' chemotherapy regimens should be similar to that used in the treatment of relapsed DLBCL (Chaganti et al, 2016). Given the young age of presentation combined with infrequent bone marrow involvement at relapse (Bishop et al, 1999), it is suggested that high dose therapy (HDT)/ASCT should be considered with curative intent, albeit there is a paucity of published outcome data in the rituximab era.

The importance of chemosensitive disease prior to HDT/ASCT was identified in the pre-rituximab era (Kuruvilla et al, 2008), and this has been reinforced by recent data published by the European Society for Blood and Marrow Transplantation (EBMT) (Avivi et al, 2017).

In their retrospective study, 86 patients had received HDT/ASCT and the majority had prior rituximab-containing therapy. At a median follow-up of 5 years, those patients transplanted in CR/partial remission (PR) >1 had a PFS of 64% and OS of 85% compared with 39% and 41%, respectively, for chemorefractory disease at the time of transplant. If RT has not been given previously, it can play an important part in local disease control and can be safely given pre- and post-ASCT with judicious planning of RT and careful attention to RT volume and lung doses (Lane et al, 2012).

The evidence for the role of allogeneic stem cell transplantation in PMBCL is very limited and needs to be examined in prospective clinical trials. There are many new emerging therapeutic agents, such as brentuximab vedotin (Jacobsen et al, 2015), agents directed at the PDCD1 (PD-1)/CD274 (PD-L1) axis (Zinzani et al, 2017a) and CD19 chimeric antigen receptor (CAR)-T cell therapy (Neelapu et al, 2017), which may have a role in salvage therapy in the future, but currently the evidence for their use in PMBCL is sparse (Jacobsen et al, 2015) and, in the case of brentuximab vedotin, conflicting data of its proposed efficacy in PBMCL have been reported (Zinzani et al, 2017b). Participation in a clinical trial should be considered.

Referenzen

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Gilson D et al., 2019 [4].

British Association of Dermatologists (BAD)

British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018.

Zielsetzung

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations on the management of primary cutaneous lymphoma in the U.K. The document aims to: (i) offer an appraisal of all relevant literature up to February 2018 focusing on any key developments; (ii) address important, practical clinical questions

relating to the primary guideline objective; (iii) provide guideline recommendations with, where appropriate, some health economic implications; and (iv) discuss potential developments and future directions.

Methodik

Grundlage der Leitlinie

- Keine Beteiligung von Patientenvertretungen an der Leitlinienerstellung, lediglich zur externen Begutachtung vorgelegt,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematik der Suche und Auswahl der Literatur dargelegt, kritische Bewertung erwähnt, aber keine Details beschrieben,
- Konsensfindung erwähnt, aber nicht detailliert beschrieben, externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig, die Verknüpfung mit der Evidenz ist nur indirekt über den Hintergrundtext zu den Empfehlungen möglich, Evidenzgrade fehlen,
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

Targeted literature searches were carried out in the PubMed, MEDLINE and Embase databases and the Cochrane Library […] to February 2018. […] Additional relevant references were also retrieved from citations in the reviewed literature.

LoE

Tabelle 6: Levels of Evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal*
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus
* Studies with a level of evidence '–' should not be used as a basis for making a recommendation.	

GoR

Tabelle 7: Strength of Recommendation

Class	Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or A systematic reviw of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

Recommendations

8.2.2 Primary cutaneous diffuse large B-cell lymphoma (not otherwise specified)

PCLBCL (NOS) includes rare morphological variants ot DLBCL such as anaplastic lymphoma, plasmablastic lymphoma, T-cell/histiocyte rich large B-cell lymphoma and intravascular large B-cell lymphoma, which may rarely present primarily in the skin.3 These variants should be treated with systemic lymphoma chemotherapy protocols.

Referenzen

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6. National Comprehensive Cancer Network. NCCN guidelines. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp (last accessed 8 October 2018).

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259. Fenot M, Quereux G, Brocard A, Renaut JJ, Dreno B. Rituximab for primary cutaneous diffuse large B-cell lymphoma – leg type. Eur J Dermatol 2010;20(6):753-757.

National Comprehensive Cancer Network (NCCN), 2022 [8].

B-Cell Lymphomas; Vers. 03.2022.

Zielsetzung

The National Comprehensive Cancer Network (NCCN®) Guidelines (NCCN® Guidelines) were developed […] with the aim to provide recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL […].

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund limitierter höherwertiger Evidenz, zu Behandlungsmethoden für Patientinnen und Patienten mit einem FL3B und Subentitäten des DLBCL, wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt (⇨ NCCN Guidelines Panel Disclosures)
- Systematische Suche erwähnt, aber keine Details beschrieben (z. B. Suchzeitraum), keine Angaben zur systematischen Auswahl und Bewertung der Evidenz,
- Konsensfindung erwähnt, aber nicht detailliert beschrieben, externes Begutachtungsverfahren nicht dargelegt,
- Empfehlungen der Leitlinie sind eindeutig, Literaturverknüpfung mit Evidenzbewertung im Hintergrundtext[3],
- Weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

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

LoE/GoR

Tabelle 9: NCCN Categories of Evidence and Consensus

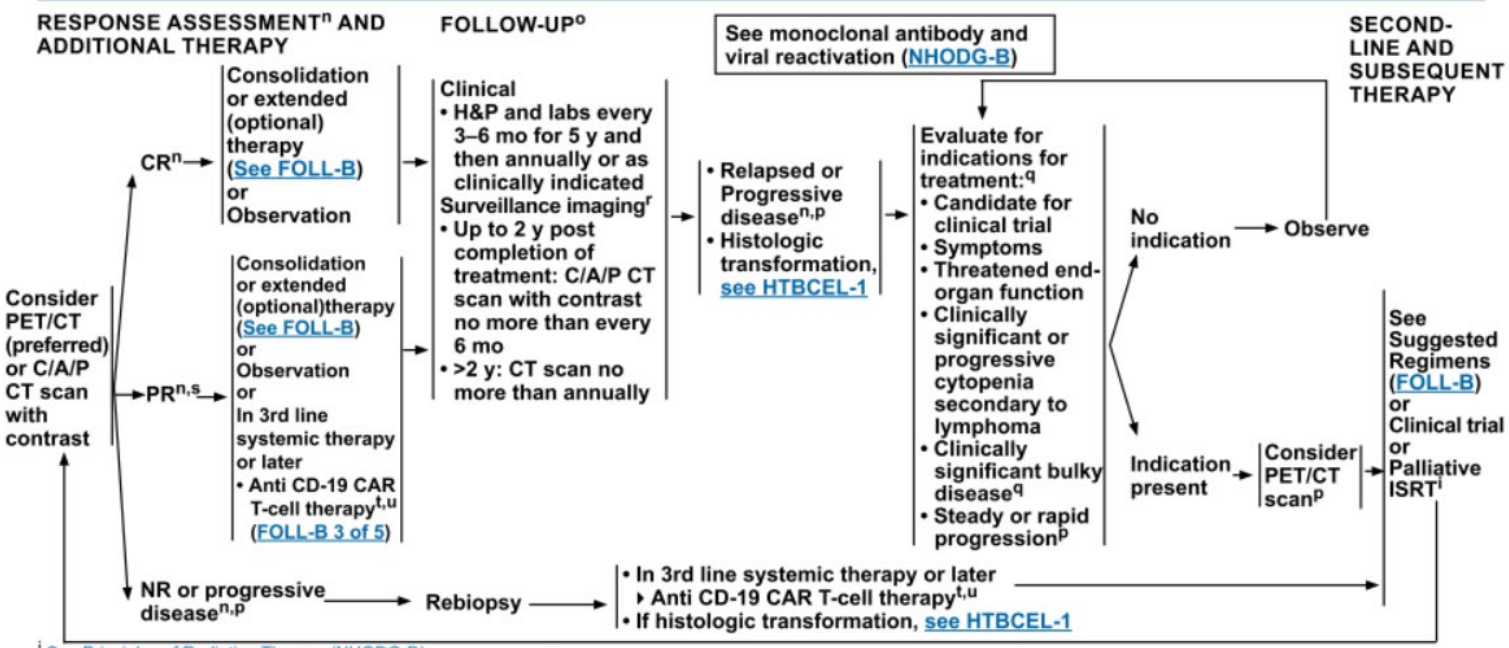
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that 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.

[3] Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Recommendations

Follicular Lymphoma



[i] See Principles of Radiation Therapy (NHODG-D).
[n] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[o] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated. Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[p] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (FOLL-6).
[q] See GELF criteria (FOLL-A).
[r] Surveillance imaging is used for monitoring asymptomatic patients. When a site of disease can only be visualized on PET/CT scan (eg, bone), it is appropriate to proceed with PET/CT scans for surveillance.
[s] A PET-positive PR is associated with a shortened PFS (See Discussion); however, additional treatment at this juncture has not been shown to change outcome.
[t] This includes ≥2 of chemoimmunotherapy regimens. For example, prior treatment with BR and RCHOP.
[u] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).

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.

FOLL-5

SUGGESTED TREATMENT REGIMENS[a]

An FDA-approved biosimilar is an appropriate substitute for rituximab.[c]

SECOND-LINE THERAPY[j]

Preferred regimens (in alphabetical order)
- Bendamustine[k,l] + obinutuzumab[m] or rituximab (not recommended if treated with prior bendamustine)
- CHOP + obinutuzumab[m] or rituximab
- CVP + obinutuzumab[m] or rituximab
- Lenalidomide + rituximab

Other recommended regimens (in alphabetical order)
- Ibritumomab tiuxetan[g]
- Lenalidomide (if not a candidate for anti-CD20 monoclonal antibody therapy)
- Lenalidomide + obinutuzumab
- Obinutuzumab
- Rituximab
- See Second-line Therapy for DLBCL (BCEL-C 2 of 6) without regard to transplantability[n]

SECOND-LINE THERAPY FOR ELDERLY OR INFIRM
(if none of the therapies is expected to be tolerable in the opinion of treating physician)

Preferred regimen
- Rituximab (375 mg/m^2 weekly for 4 doses)

Other recommended regimens
- Chlorambucil ± rituximab
- Cyclophosphamide ± rituximab
- Tazemetostat (EZH2 wild type or unknown relapsed/refractory disease in patients who have no satisfactory alternative treatment options)
- Ibritumomab tiuxetan[g] (category 2B)

SECOND-LINE CONSOLIDATION OR EXTENDED DOSING (optional)

Preferred regimens
- Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1)
- Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

Other recommended regimens
- High-dose therapy with autologous stem cell rescue
- Allogeneic hematopoietic cell transplant in selected cases[o]

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

See Third-Line and Subsequent Therapy (FOLL-B 3 of 5)
See Footnotes on FOLL-B 3 of 5

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.

SUGGESTED TREATMENT REGIMENS[a]

An FDA-approved biosimilar is an appropriate substitute for rituximab.[c]

THIRD-LINE AND SUBSEQUENT THERAPY[p]

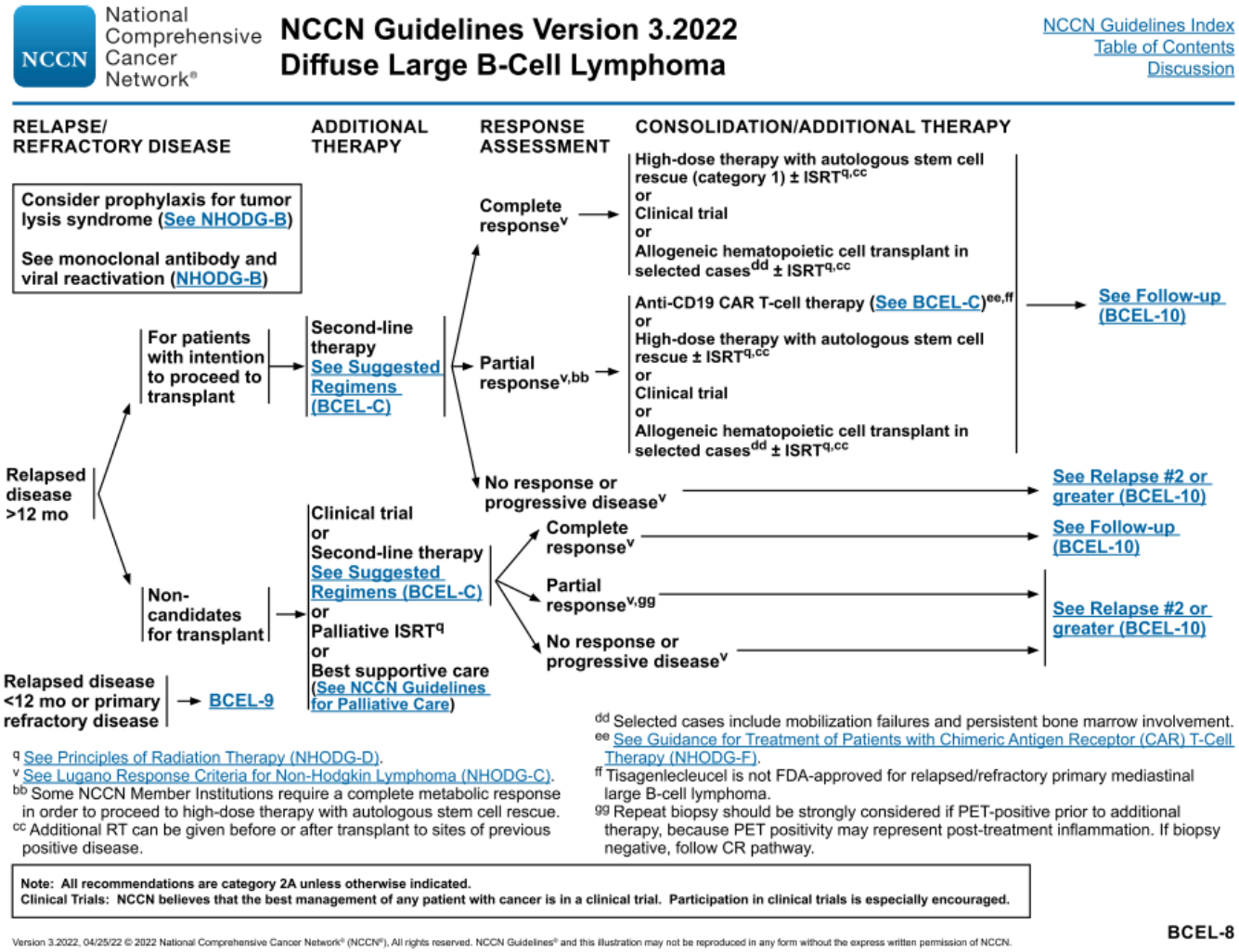
- **PI3K inhibitors (in alphabetical order)**
  - **Copanlisib[q]**
- **EZH2 inhibitor**
  - **Tazemetostat**
    - ***EZH2* mutation positive**
    - ***EZH2* wild type or unknown relapsed/refractory disease in patients who have no satisfactory alternative treatment options**
- **Anti CD-19 CAR T-cell Therapy**
  - **Axicabtagene ciloleucel[r]**

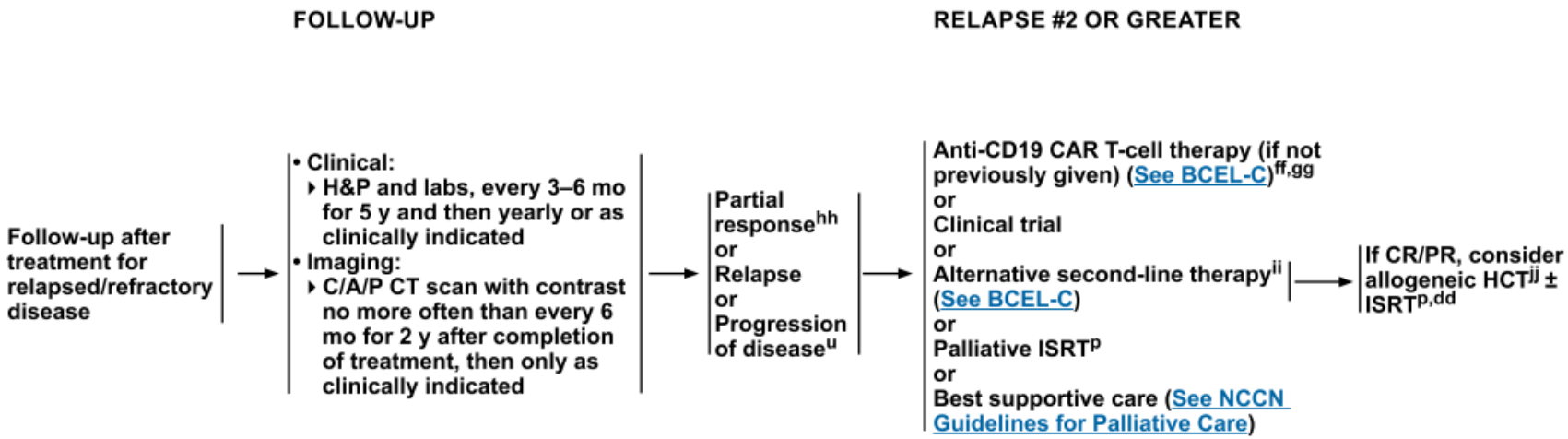
[a] See references for regimens on FOLL-B 4 of 5 and FOLL-B 5 of 5.
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[g] Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for ibritumomab tiuxetan. If ibritumomab tiuxetan is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT. Cytogenetics/FISH assessment for MDS markers is recommended for patients receiving RIT.
[j] Generally, a first-line regimen is not repeated.
[k] Prophylaxis for PJP and VZV should be administered; see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[l] In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.
[m] The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data. Obinutuzumab is preferred in patients with rituximab refractory disease, which includes disease progressing on or within 6 months of prior rituximab therapy
[n] Brentuximab vedotin and ibrutinib are not options for second-line therapy for follicular lymphoma.
[o] Selected cases include mobilization failures and persistent bone marrow involvement.
[p] Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 5) that were not previously used.
[q] See Special Considerations for the Use of Small-Molecule Inhibitors (NHODG-E).
[r] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).

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.

FOLL-B 3 OF 5

Diffuse Large B-Cell Lymphoma





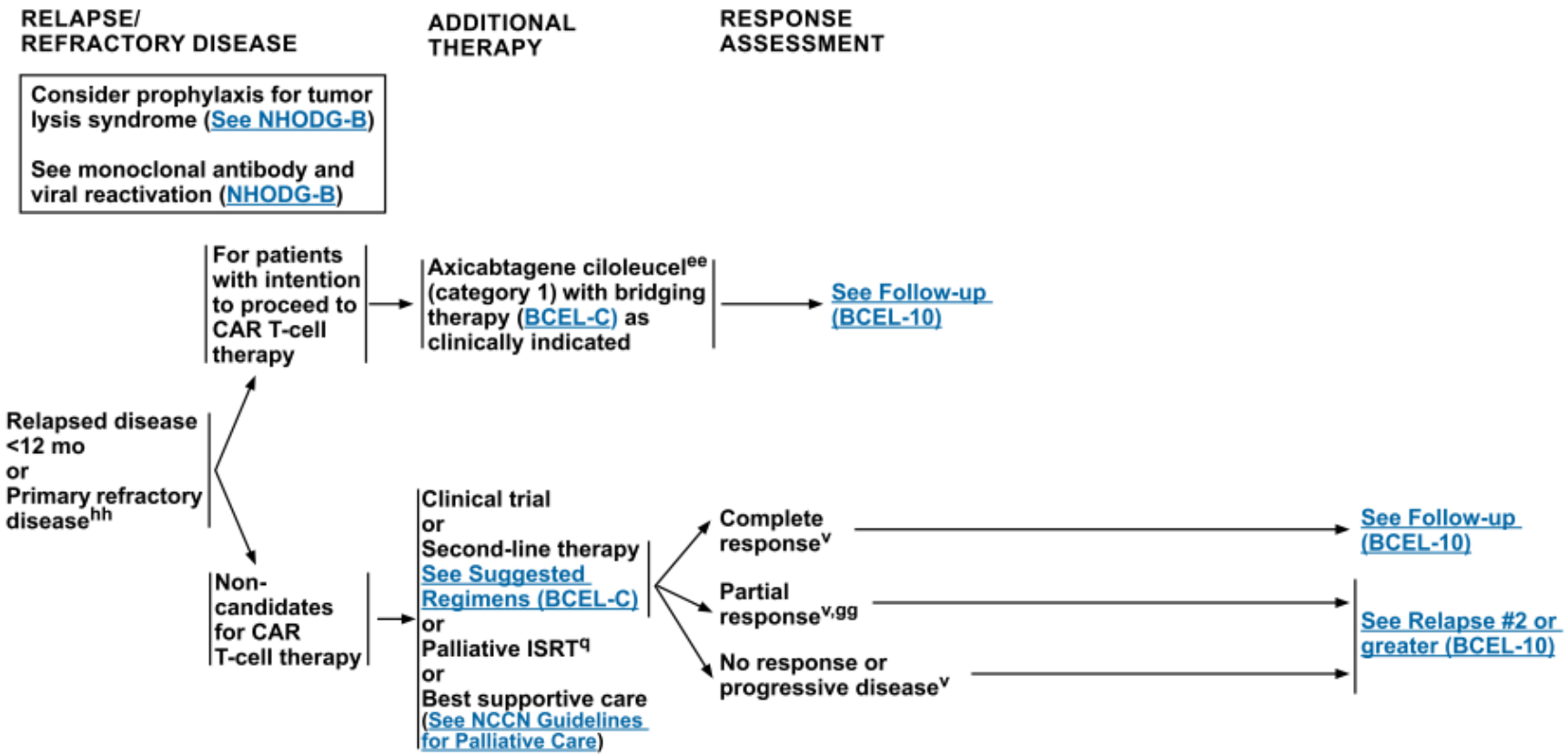
Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[p] See Principles of Radiation Therapy (NHODG-D).
[u] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).
[dd] Additional RT can be given before or after transplant to sites of previous positive disease.
[ff] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[gg] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[hh] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
[ii] Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.
[jj] Patients achieving high-quality CR/PR following alternative second-line therapy may benefit from an allogeneic HCT.

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.

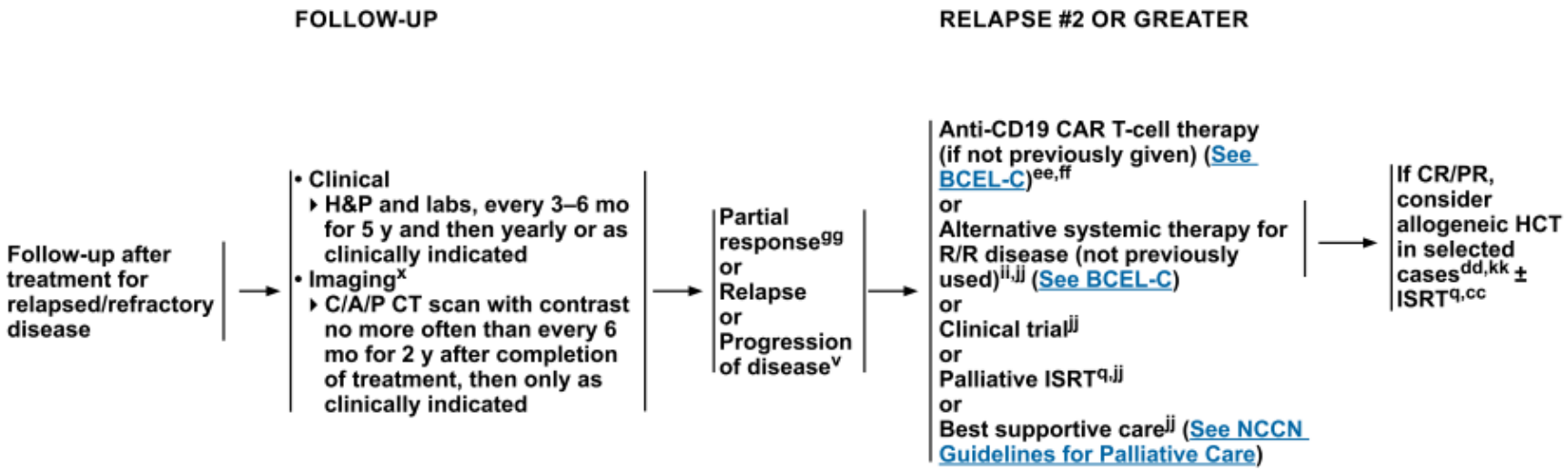
BCEL-8



[q] See Principles of Radiation Therapy (NHODG-D).
[v] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).
[ee] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[gg] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
[hh] Management of localized refractory disease is uncertain. RT ± chemoimmunotherapy followed by high-dose therapy with stem cell rescue may be an option for some patients.

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.

BCEL-9



Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[q] See Principles of Radiation Therapy (NHODG-D).
[v] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).
[x] Surveillance imaging is used for monitoring asymptomatic patients. When a site of disease can only be visualized on PET/CT scan (eg, bone), it is appropriate to proceed with PET/CT scans for surveillance.
[cc] Additional RT can be given before or after transplant to sites of previous positive disease.
[dd] Selected cases include mobilization failures and persistent bone marrow involvement.
[ee] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[ff] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[gg] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
[ii] Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.
[jj] If not a candidate for CAR T-cell therapy.
[kk] Patients achieving high-quality CR/PR following alternative second-line therapy may benefit from an allogeneic HCT.

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.

BCEL-10

SUGGESTED TREATMENT REGIMENS[a]

An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

SECOND-LINE THERAPY[d,i,j] (intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Other recommended regimens (in alphabetical order)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

SECOND-LINE THERAPY[d,i,j] (non-candidates for transplant)

Preferred regimens (in alphabetical order)
- GemOx ± rituximab
- Polatuzumab vedotin-piiq ± bendamustine ± rituximab[k,l]
- Tafasitamab-cxix[m] + lenalidomide

Other recommended regimens (in alphabetical order)
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- Gemcitabine, vinorelbine ± rituximab (category 3)
- Rituximab

Useful in certain circumstances
- Brentuximab vedotin for CD30+ disease[n]
- Bendamustine[k] ± rituximab (category 2B)
- Ibrutinib[n,o] (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

CAR T-CELL THERAPY BRIDGING OPTIONS

Typically 1 or more cycles as necessary until CAR T-Cell product is available
- DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- Polatuzumab vedotin-piiq ± rituximab ± bendamustine (bendamustine should be considered/added only after leukapheresis)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

See First-line Therapy on BCEL-C 1 of 6.

See Third-Line and Subsequent Therapy on BCEL-C 3 of 6.

See Footnotes on BCEL-C 4 of 6.

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.

SUGGESTED TREATMENT REGIMENS[a]

CONSOLIDATION AFTER ALTERNATE SECOND-LINE THERAPY

- Allogeneic hematopoietic cell transplant in selected cases[p] for CR/PR following alternative second-line therapy

THIRD-LINE AND SUBSEQUENT THERAPY[q]

- Anti-CD19 CAR T-cell therapy[r]
  - Axicabtagene ciloleucel
  - Lisocabtagene maraleucel
  - Tisagenlecleucel[s]
- Loncastuximab tesirine-lpyl[m,t]
- Selinexor (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy)[u]

See First-line Therapy on BCEL-C 1 of 6.
See Second-line Therapy on BCEL-C 2 of 6.
See Footnotes on BCEL-C 4 of 6.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Histologic Transformation of Indolent Lymphomas to DLBCL

NCCN Guidelines Index
Table of Contents
Discussion

HISTOLOGIC TRANSFORMATION OF INDOLENT LYMPHOMAS TO DLBCL

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Histologic transformation of FL to DLBCL after minimal or no prior therapy[a,b,c]

- **With double hit[f]** → **Treatment regimens as listed on HGBL-1**
- **Without double hit[f]** → **Chemoimmunotherapy (anthracycline-based regimens preferred unless contraindicated) (See BCEL-C, first-line therapy) ± ISRT[g,h]**

Histologic transformation of MZL to DLBCL after minimal or no prior therapy[b,c] → **Chemoimmunotherapy (anthracycline-based regimens preferred unless contraindicated) (See BCEL-C, first-line therapy) ± ISRT[g,h]**

Histologic transformation of FL or MZL to DLBCL after multiple lines of prior therapies[d,e] → **See HTBCEL-3**

PET/CT → **See Response to Therapy (HTBCEL-2)**

[a] Perform FISH for BCL2 rearrangement [t(14;18)], and MYC rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[b] ISRT alone or one course of single-agent therapy including rituximab.
[c] NGS may be useful for treatment selection.
[d] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.
[e] Perform FISH for BCL6 and MYC rearrangements.
[f] In the 2017 revised WHO classification of lymphomas, DLBCL, double hit has been designated in a unique category called high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6.
[g] See Principles of Radiation Therapy (NHODG-D).
[h] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.

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.

HISTOLOGIC TRANSFORMATION OF FL OR MZL TO DLBCL (AFTER MINIMAL OR NO PRIOR THERAPY)

RESPONSE TO THERAPY

CR[j,k] → **Observation[i] or Clinical trial** → **Relapsed disease[k]** → **Biopsy[l]** → **See Histologic Transformation of FL or MZL to DLBCL After Multiple Prior Therapies (HTBCEL-3)**

PR[j,k] or NR or progressive disease[j] → **Second-line therapy**
See HTBCEL-A for suggested systemic therapy regimens. Selection of treatment must be based on transplant eligibility. → **Response Assessment and Additional Therapy (HTBCEL-3)**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[i] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated. Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[j] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[k] If transformation is coexisting with extensive FL, consider maintenance (see FOLL-5, Optional Extended Therapy).
[l] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per FOLL-5. If biopsy negative, follow CR pathway.

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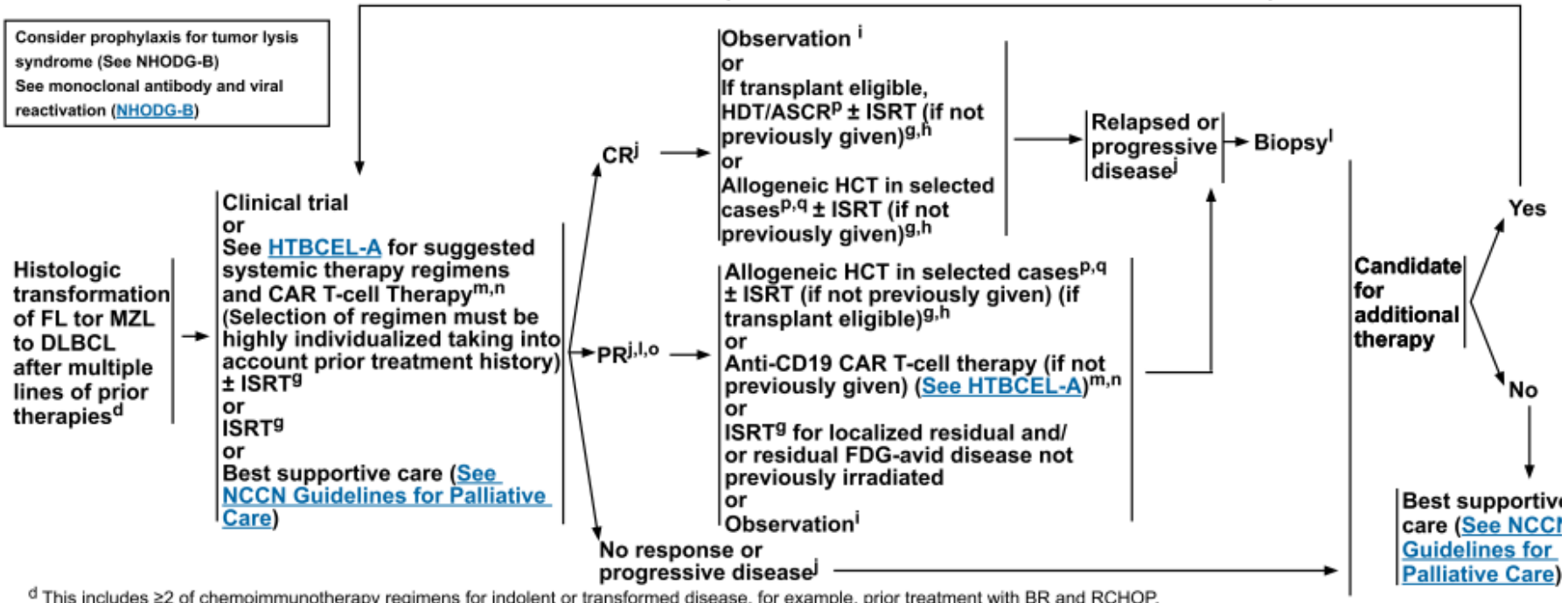
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HISTOLOGIC TRANSFORMATION OF FL AND MZL TO DLBCL (AFTER MULTIPLE LINES OF PRIOR THERAPIES)[d]



[d] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease, for example, prior treatment with BR and RCHOP.
[g] See Principles of Radiation Therapy (NHODG-D).
[h] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[i] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated. Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[j] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[l] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per FOLL-5. If biopsy negative, follow CR pathway.
[m] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.
[n] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[o] If proceeding to transplant, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Anti-CD19 CAR T-cell therapy is not an appropriate treatment option for patients in CR.
[p] Data on transplant after treatment with anti-CD19 CAR T-cell therapy are not available. HDT/ASCR is not recommended after anti-CD19 CAR T-cell therapy. Allogeneic HCT could be considered but remains investigational.
[q] Selected cases include mobilization failures and persistent bone marrow involvement.

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HTBCEL-3

SUGGESTED TREATMENT REGIMENS[a]

An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

SYSTEMIC THERAPY REGIMENS[c]		
Intention to proceed to transplant	**Preferred regimens** • RCHOP (if not previously given) • If previously treated with anthracycline-based regimen (in alphabetical order) ▸ DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab ▸ GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab ▸ ICE (ifosfamide, carboplatin, etoposide) ± rituximab	
Non-candidates for transplant	**Preferred regimens** • RCHOP (if not previously given) • If previously treated with anthracycline-based regimen (in alphabetical order) ▸ GemOx ± rituximab ▸ Polatuzumab vedotin-piiq ± bendamustine ± rituximab[d,e] ▸ Tafasitamab-cxix[f] + lenalidomide	**Other recommended regimens** (in alphabetical order) • CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab • GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab • Loncastuximab tesirine-lpyl[f,g]

ANTI-CD19 CAR T-CELL THERAPY[h,i]
• Histologic transfromation of FL or MZL (all subtypes) ▸ Lisocabtagene maraleucel • Histologic transfromation of FL or nodal MZL ▸ Axicabtagene ciloleucel ▸ Tisagenlecleucel

[a] See references for regimens on HTBCEL-A 2 of 2.
[b] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[c] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[d] In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.
[e] Bendamustine, rituximab, and polatuzumab vedotin-piiq is indicated for the treatment of adult patients with relapsed or refractory DLBCL or HGBL with translocations of MYC and BCL2 and/or BCL
[f] It is unclear if tafasitamab or loncastuximab tesirine or if any other CD-19 directed therapy would have a negative impact on the efficacy of subsequent anti- CD19 CAR T-cell therapy.
[g] Loncastuximab tesirine is FDA approved for relapsed or refractory DLBCL, high-grade B-cell lymphoma (HGBL) with translocation of *MYC* and *BCL2* and/or *BCL6* (double-/triple-hit lymphoma), and HGBL, NOS, as well as DLBCL arising from FL and MZL.
[h] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[i] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

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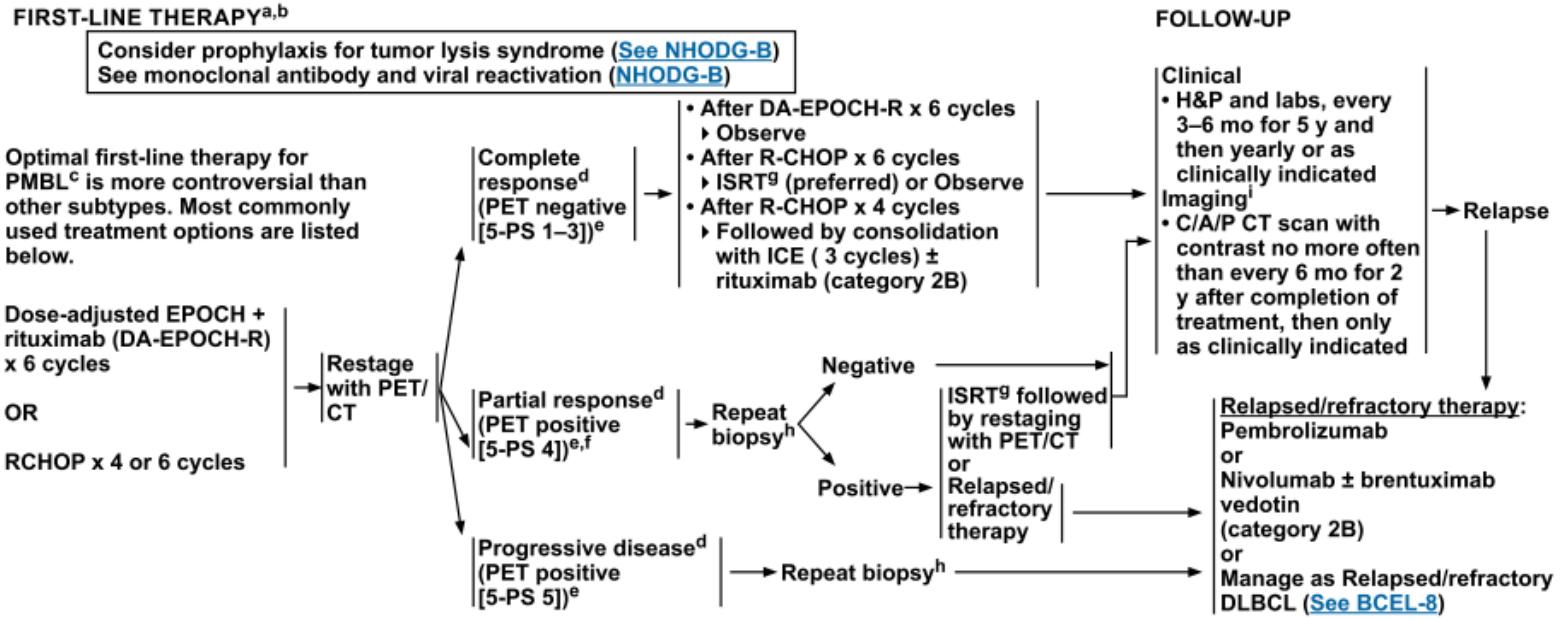
HTBCEL-A
1 OF 2

Primary Mediastinal Large B-Cell Lymphoma



[a] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[b] An FDA-approved biosimilar is an appropriate substitute for rituximab.

[c] Primary mediastinal large B-cell lymphoma (PMBL) can be defined as a clinical entity presenting with primary site of disease in the anterior mediastinum with or without other sites and has histology of DLBCL. Clinical pathologic correlation is required to establish diagnosis. PMBL overlaps with gray zone lymphomas that have intermediate features between Hodgkin lymphoma and PMBL and have unique diagnostic characteristics. See Gray Zone Lymphoma (BCEL-B 2 of 3). See Special Considerations for Adolescent and Young Adult Patients (AYA) with B-Cell Lymphomas (NHODG-B 5 of 5)

[d] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).

[e] PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS) (See NHODG-C 3 of 3).

[f] Persistent PET/CT positive masses at end-of-treatment after DA-EPOCH-R (5PS 4 and on visual inspection demonstrate minimal uptake above liver) can be observed (with follow-up scans) without biopsy.

[g] See Principles of Radiation Therapy (NHODG-D).

[h] Residual mediastinal masses are common. PET/CT scan is essential post-treatment. Biopsy of PET/CT scan positive mass is recommended if additional systemic treatment is contemplated.

[i] Surveillance imaging is used for monitoring asymptomatic patients. When a site of disease can only be visualized on PET/CT scan (eg, bone), it is appropriate to proceed with PET/CT scans for surveillance.

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.

PMBL-1

Alberta Provincial Thoracic Tumour Team, 2019[1].

Lymphoma.

Fragestellungen

- What are the diagnostic criteria for the most common lymphomas?
- What are the staging and re-staging procedures for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended treatment and management options for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended follow-up procedures for patients with malignant Hodgkin and non-Hodgkin lymphoma?

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund limitierter höherwertiger Evidenz, zu Behandlungsmethoden für Patientinnen und Patienten mit einem FL3B und Subentitäten des DLBCL, wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, aber keine Einbeziehung von Patientenvertretungen,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Angaben zur systematischen Auswahl und kritischen Bewertung der Literatur fehlen[4],
- Verfahren zur Konsensfindung (formal und informell) erwähnt, externes Begutachtungsverfahren nicht dargelegt,
- Empfehlungen der Leitlinie sind identifizierbar, Angaben zu Literaturverknüpfungen, Evidenzbewertung und Graduierung der Empfehlungen fehlen,
- Beschreibung des Verfahrens zur Überwachung und Aktualisierung ist widersprüchlich[5].

Recherche/Suchzeitraum:

Medical journal articles were searched using Medline (1950 to October Week 1, 2015), EMBASE (1980 to October Week 1, 2015), Cochrane Database of Systematic Reviews (3rd Quarter, 2015), and PubMed electronic databases. An updated review of the relevant existing practice guidelines for lymphoma was also conducted by accessing the websites of the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), the European Society for Medical Oncology (ESMO), and the British Committee for Standards in Haematology.

[4] Updated evidence was selected and reviewed by members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit.

[5] A formal review of the guideline will be conducted at the Annual Provincial Hematology Tumour Team Meeting in 2015. If critical new evidence is brought forward before that time […] the guideline working group members will revise and update the document accordingly. (siehe 'Maintenance')

The original guideline was developed in March 2006 and was revised on the following dates: May 2007, June 2009, November 2009, January 2011, December 2011, September 2012, April 2013, December 2014, December 2015, February 2016 and April 2016. (siehe 'Development and Revision History')

LoE

Tabelle 10: Levels of Evidence

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

GoR

Tabelle 11: Strength of Recommendations

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

Sonstige methodische Hinweise

Die Feststellung der Stärke der Evidenz und eine Graduierung der Empfehlungen nach dem oben aufgeführten Klassifikationsschema erfolgt bei der Leitlinienerstellung durch das Alberta Provincal Hematology Tumour Team, gemäß Methodenpapier, erst seit Ende 2019.

Recommendations

III. Treatment of non-Hodgkin Lymphomas

Treatment of relapsed DLBCL

All patients younger than 65-70 years of age who experience disease persistence or progression after initial RCHOP chemotherapy should be considered for high dose salvage therapy with autologous stem cell transplantation (SCT). These patients should be referred to the BMT clinic as soon as possible, or a transplant physician should be contacted directly to discuss management decisions. Often these patients will require special salvage therapy recommendations that may necessitate management by the transplant program in a hospital setting (e.g., R-DICEP or R-MICE). Potential transplant candidates should receive rituximab with the salvage chemotherapy to maximize the chance of response, and in-vivo purge blood of tumour cells. Other patients who are not transplant candidates could receive conventional salvage therapy regimens such as DHAP, ICE, GDP, CEPP or MEP. Amongst these options, GDP is generally preferred because it can be given on an outpatient basis. Prognosis of relapsed DLBCL patients who do not undergo high-dose chemotherapy (HDCT) and SCT is extremely poor, with median survival rates of less than 6 months. Palliation is the main goal for non-transplant candidates. Involved field radiotherapy (IFRT) to symptomatic sites may also benefit palliative patients. Third-line chemotherapy for relapsed DLBCL is rarely of benefit. If done, there has usually been a definite response to second line therapy, with disease control during and for a few months after the second-line treatment finished. Some palliative patients at or beyond second relapse may have symptomatic benefit from prednisone alone, or low dose daily oral chemotherapy with chlorambucil 0.1 mg/kg/day or etoposide 50 mg/day, or combination oral therapy such as PEPC.

Treatment of special DLBCL entities

Double Hit Lymphoma with MYC and BCL2 mutations/rearrangements by FISH

The largest multicentre retrospective analysis of 311 double hit lymphoma patients reported an OS rate of <50% if IPI=2-5 vs 65% for IPI=0-1, and >80% if IPI=0 (Petrich et al. 2014). In addition, the OS rate was approximately 90% for 39 patients who achieved CR following induction chemotherapy and then underwent SCT compared to 60% for 112 patients who achieved CR but did not receive SCT. Although this numerical difference was not statistically significant (p=0.1), it was very clinically significant, indicating that the study was underpowered to draw any meaningful conclusions regarding the role of ASCT consolidation. More recently, Landsburg et al. (2017) reported outcomes of 159 patients with Double-Hit lymphoma who achieve CR following induction therapy. This study demonstrated that PFS and OS were superior with an intensive regimen relative to RCHOP, and that ASCT only improve outcomes for patients who initially received RCHOP, but not an intensive regimen. These studies suggest that DHL patients treated with RCHOP should be considered for ASCT consolidation, especially with IPI=2-5 at diagnosis, however other patients who achieve CR after an intensive induction regimen (such as DA-EPOCH-R or R-CODOXM/IVAC) probably should not receive ASCT consolidation. Due to the lack of prospective randomized controlled studies, however, it is impossible to determine if the optimal approach involves RCHOP induction followed by ASCT or an intensive induction chemotherapy regimen.

Alberta Recommendations for special DLBCL entities

1. DLBCL with MYC translocated by FISH

- MYC-rearranged DLBCL (or intermediate between DLBCL and Burkitt lymphoma) but no translocation of BCL2 or BCL6: R-CHOP x 6 cycles for most patients. However, for the

poor prognosis situation of MYC mutated and age <70 years and IPI 4-5: R-CHOP x 4 then RDHAP or RDICEP x 1, then HDCT/ASCT. Alternatively, R-CODOX-M/IVAC or DA-EPOCH-R should be considered

- MYC rearranged and BCL2 or BCL6 rearranged (double hit) or BCL2 and BCL6 rearranged (triple hit):

IPI=0-1

⇨ RCHOP or with HDMTX after cycles 2, 4, 6 or

⇨ DA-EPOCH-R

IPI=2-5

⇨ RCHOP with HDMTX after cycles 2 (± 4) then RDICEP x 1 then HDCT/ASCT using CNS penetrating regimen with either R-BuMel/ASCT or R-MelTBI/ASCT (not BEAM)

Note: It is difficult to mobilize autologous blood stem cells after multiple cycles of intensive chemotherapy + G-CSF (RCODOXM/IVAC), particularly for older patients. Therefore, if the goal is to proceed to transplant, then RCHOP x 4 + HDMT x 2 is generally preferred for patients >60 years, or those who received prior chemotherapy for indolent lymphoma in the past and now have transformed disease.

⇨ DA-EPOCH-R or R-CODOX-M/IVAC

2. Intermediate between DLBCL and Hodgkin lymphoma:

- RCHOP x 6 cycles for most patients
- RCHOP followed by ASCT if high risk factors are present (IPI=3-5)

Referenzen

Landsburg DJ, Falkiewicz MK, Maly J, Blum KA, Howlett C, Feldman T, et al. Outcomes of patients with double-hit lymphoma who achieve frist complete remission. J Clin Oncol 2017;35(20):2260-2267.

Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014;124(15):2354-2361.

Primary Mediastinal B-Cell Lymphoma

Primary mediastinal B-cell lymphoma (PMBCL) of thymic origin represents 6-10% of all DLBCLs, and most commonly affects young adults (median age ~35), women more than men61. It frequently is associated with a bulky mediastinal mass that directly extends into extranodal thoracic tissues such as pleura, pericardium and chest wall, but rarely involves the marrow or intra-abdominal sites. Overall, PMBCL is associated with a better prognosis than other DLBCLs, including GCB DLBCLs. The IPI score tends not to work well for PMBCL because most patients are young with fairly well preserved performance status, and have elevated LDH. Therefore, limited vs advanced stage, and number extranodal sites (especially pleural effusions) tend to be the only factors that subdivide patients into excellent vs good prognosis. Likewise, because most patients have a very good prognosis, interim or end of treatment restaging PET imaging is associated with very high negative predictive value, but relatively low positive predictive value62. Therefore, a positive restaging PET scan should probably not be used alone to guide further therapy.

Treatment of PMBCL with RCHOP ± IFRT is associated with cure rates of approximately 75% and overall survival rates of 90%. Phase II studies have reported that intensifying chemotherapy (eg. dose adjusted EPOCH-R) maintains excellent outcomes while avoiding

IFRT, but there are no phase III randomized controlled trials that prove DA-EPOCH-R is superior to RCHOP, or even that IFRT after RCHOP improves survival rates relative to RCHOP alone. The latter is studied in the ongoing IELSG-37 clinical trial. A large retrospective study from 11 centres compared outcomes of 132 PMBCL patients treated with RCHOP (n=56) or with dose-adjusted R-EPOCH (n=76), and found similar survival rates of approximately 90% with both regimens63. The prospective phase III CALGB/Alliance 50303 study randomized 464 DLBCL (including ~6% PMBCL) patients to RCHOP or DA-EPOCH-R, and found no difference in EFS or OS between regimens, although there was substantially more toxicity with DA-EPOCH-R. Unpublished retrospective real world data for 50 consecutive patients in Alberta treated with RCHOP from 2005-2017 found a long-term overall survival rate of approximately 90% regardless of limited (n=33) or advanced (n=17) stage at diagnosis, and regardless of treatment with (n=30) or without (n=20) IFRT. The OS rate was 100% for the 13 limited stage patients treated with RCHOP alone, without IFRT.

In conclusion, available evidence supports the use of RCHOP for patients with PMBCL, and does not support the use of DA-EPOCH-R. In view of the long term risk of secondary malignancy and premature heart disease from IFRT in young patients, IFRT should probably be restricted to those with bulky masses >10 cm at diagnosis that do not respond well to chemotherapy (eg. <50% response and could also be considered for patients with positive end of treatment PET/CT).

Referenzen

61. Martelli M, Ferreri A, Di Rocci A, Ansuinelli M, Johnson PWM. Primary mediastinal large B-cell lymphoma. Crit Rev Oncol Hematol 2017;113:318-327.

62. Lazarovici J, Terroir M, Arfi-Rouche J, Michot JM, Mussot S, Florea V, et al. Poor predictive value of positive interim FDG-PET/CT in primary mediastinal large B-cell lymphoma. Eur J Nucl Med Mol Imaging 2017;44(12):2018-2024.

63. Shah NN, Szabo A, Huntington SF, Epperla N, Reddy N, Ganguly S, et al. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis. Br J Haematol 2018;180(4):534-544.

Follicular Lymphoma

For grade 3b follicular lymphoma or DLBCL with areas of follicular lymphoma, R-CHOP should be used. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

Therapy of relapsed disease. Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma, including: • Patient Factors: Age, co-morbidity, symptoms, short vs. long-term goals, preservation of future options, reimbursement/ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (RR, PFS, OS).

Disease Factors: Stage, sites of involvement, grade, transformation, prior therapy, time from prior therapy (disease-free interval).

Evidenbasis:

For example, previously healthy patients younger than 70 years who relapse within 2 years of initial chemotherapy have a median life expectancy of <5 years, and are best managed with HDCT/ autologous SCT. HDCT/SCT maximizes the length of disease control for all patients less than 70 years, regardless of length of initial remission, and as such is a reasonable treatment option for those who accept potential risks/toxicities. Therefore, patients younger than 70 years without serious co-morbid disease, and who respond to salvage therapy should be considered for high dose chemotherapy and autologous (relapse 12) or allogeneic stem cell transplantation (relapse 3). A large retrospective study of consecutively treated relapsed follicular lymphoma patients in Alberta and BC reported 5 year overall survival rates following relapse of ~90% for

those who received ASCT vs ~60% for those who did not receive ASCT. This marked difference in survival retained significance in multivariate as well as instrumental variable analyses112.

Conversely, some patients may be best managed by repeating their initial treatment regimen, especially if they achieved an initial remission greater than 5 years. Other patients should be changed to a second line standard-dose chemotherapy regimen (bendamustine, chlorambucil, CVP, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). For patients who have rituximab, it is reasonable to re-treat with rituximab alone or with chemotherapy as long as the patient attained at least a 6 month remission to prior rituximabbased therapy. Rituximab maintenance should only be used once in the course of a patient's disease (first remission or first relapse). Palliative, symptomatic care (possibly including palliative IFRT 4Gy/2 fractions) is usually the best option for patients who were refractory to their 2 most recent treatment regimens, those with CNS involvement, or those with an ECOG score of 3-4.

A phase 3, open-label, two-arm parallel, randomized trial (GADOLIN), compared obinutuzumab and bendamustine followed by obinutuzumab maintenance to bendamustine alone in patients with rituximabrefractory, indolent non-Hodgkin lymphoma (failure to respond or progress during or within 6 months of a rituximab containing regimen). The primary outcome was PFS, and other outcomes included OS, overall response, duration of response, quality of life, and adverse events. In the subgroup of patients with follicular lymphoma, the median PFS was 25.3 months in patients treated with obinutuzumab plus bendamustine versus 14 months in patients treated with bendamustine alone (HR[95%CI]: 0.52[0.39,0.69]; p<0.0001). From the April 2016 data cut-off, median OS for obinutuzumab plus bendamustine was not estimable (NE) and median OS for bendamustine alone was 53.9 months (40.9 to NE) (HR[95%CI: 0.58[0.39.0.86]; p=0.0061). While there was no significant advantage reported for patients with other subtypes of iNHL, this was deemed to be based purely on the small numbers in other subgroups. Based on these results, it is recommended that obinutuzumab chemo-immunotherapy be considered in patients with rituximab-refractory iNHL. While the study used bendamustine as a chemotherapy backbone, few patients on the study had received bendamustine as their frontline therapy. Given current practice to use BR for the frontline treatment of FL and the fact that there is no biological reason that the same clinical benefit of obinutuzumab would not be seen in combination with other chemotherapies, alternate NHL chemotherapy backbones could be considered for patients deemed inappropriate for bendamustine retreatment. While there was a higher frequency of serious adverse events in the obinutuzumab plus bendamustine arm, many of these were infusion-related reactions which can be safely managed. Relatively frequent infections were also noted so prophylactic antibiotics and antivirals should be considered, especially when obinutuzumab is combined with bendamustine.

Another option to consider for rituximab-refractory relapsed FL patients is radioimmunotherapy with 90Yibritumomab tiuxetan (Zevalin). This option, however, requires Director's Privilege approval, and is not currently listed on the Alberta Cancer Drug Benefit List for funding. In a small study of 57 patients with rituximab-refractory FL (median 4 prior therapies), the overall response rate to 90Y-ibritumomab tiuxetan was 74% (CR 15%) and median duration of response of 8.7months. There may be small subset of patients (10-15%) who achieve long-term PFS following 90Y-ibritumomab tiuxetan90,113.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 05 of 12, May 2022) am 17.05.2022

#	Suchfrage
1	[mh "lymphoma, large b-cell, diffuse"]
2	diffuse:ti,ab,kw NEXT large:ti,ab,kw NEXT b-cell:ti,ab,kw NEXT lymphoma*:ti,ab,kw
3	large lymphoid lymphoma*:ti,ab,kw
4	((histiocytic OR b-cell) AND lymphoma*):ti,ab,kw
5	(dlbcl):ti,ab,kw
6	[3-5]
7	[mh "lymphoma, follicular"] OR [mh "lymphoma, non-hodgkin"]
8	((follicular OR nodular OR small cleaved cell) AND lymphoma*):ti,ab,kw
9	#7 OR #8
10	(PMBCL OR rrPMBCL OR ((primary NEXT mediastinal) AND lymphoma*)):ti,ab,kw
11	((THRBCL OR histiocyte NEXT rich OR histiocyte-rich) AND lymphoma*):ti,ab,kw
12	{OR #6, #9-#11}
13	#12 with Cochrane Library publication date from May 2017 to present

Systematic Reviews in Medline (PubMed) am 17.05.2022

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

#	Suchfrage
1	lymphoma, large b-cell, diffuse[mh]
2	diffuse[tiab] AND large[tiab] AND (b-cell[tiab] OR cell[tiab]) AND lymphoma*[tiab]
3	(histiocytic[tiab] OR (large[tiab] AND lymphoid[tiab])) AND lymphoma*[tiab]
4	DLBCL[tiab]
5	#1 OR #2 OR #3 OR #4
6	lymphoma, follicular[mh] OR lymphoma, non-hodgkin[mh:noexp]
7	(follicular[tiab] OR nodular[tiab] OR small cleaved cell[tiab]) AND lymphoma*[tiab]
8	#6 OR #7
9	PMBCL[tiab] OR rrPMBCL[tiab] OR (primary mediastinal[tiab] AND lymphoma*[tiab])
10	THRBCL[tiab] OR ((histiocyte rich[tiab] OR histiocyte-rich[tiab]) AND lymphoma*[tiab])

#	Suchfrage
11	#5 OR #8 OR #9 OR #10
12	(#11) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] 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]))))))
13	((#12) AND ("2017/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 17.05.2022

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

#	Suchfrage
1	lymphoma, large b-cell, diffuse[mh]
2	diffuse[tiab] AND large[tiab] AND (b-cell[tiab] OR cell[tiab]) AND lymphoma*[tiab]
3	(histiocytic[tiab] OR (large[tiab] AND lymphoid[tiab])) AND lymphoma*[tiab]
4	DLBCL[tiab]
5	#1 OR #2 OR #3 OR #4
6	lymphoma, follicular[mh] OR lymphoma, non-hodgkin[mh:noexp]
7	(follicular[tiab] OR nodular[tiab] OR small cleaved cell[tiab]) AND lymphoma*[tiab
8	#6 OR #7
9	PMBCL[tiab] OR rrPMBCL[tiab] OR (primary mediastinal[tiab] AND lymphoma*[tiab])
10	THRBCL[tiab] OR ((histiocyte rich[tiab] OR histiocyte-rich[tiab]) AND lymphoma*)
11	#5 OR #8 OR #9 OR #10
12	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
13	(((#12) AND ("2017/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.05.2022

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

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

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

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

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

2022-B-224-z

Kontaktdaten

Bundesärztekammer, Bereich Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 20.06.2022

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

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

Bei der beschriebenen Situation handelt es sich in der Regel bei der Erstlinientherapie um eine Behandlung mit Rituximab, Cyclophosphamid, Vincristin, Adriamycin und Prednisolon (R-CHOP) mit sechs bis acht Zyklen. Als zweite systemische Vortherapie wird im Falle eines Rezidivs bzw. bei einer refraktären Situation eine Hochdosistherapie mit autologer Stammzelltransplantation durchgeführt. Bei Notwendigkeit einer erneuten Behandlung (Progress, Refraktärität oder Rezidiv) erfolgt als nächste Behandlung entweder die allogene Stammzelltransplantation oder die Behandlung mittels CAR-T-Zellen. Dies setzt allerdings voraus, dass die Patientin bzw. der Patient keine Kontra-indikationen gegen diese Behandlung hat.

Sollte dies jedoch der Fall sein, kommen in palliativer Intention verschiedene Immun-Chemotherapie-Regime zum Einsatz. Gegeben werden kann eine Kombination aus Rituximab, Gemcitabin und Oxaliplatin, gegebenenfalls eine intensivere Behandlung mit Rituximab, Iphosphamid, Carboplatin und Etoposid (R-ICE) oder Rituximab, Dexamethason, Cisplatin und Cytarabin (R-DHAP). Auch die Kombination aus Rituximab, Bendamustin und Polatuzumab Vedotin (Pola-BR) ist möglich und zugelassen.

Der pU plant folgende spezielle Patientenpopulation zu untersuchen: DLBCL nicht weiter spezifiziert (NOS), primär mediastinales großzelliges B-Zell-Lymphom, high-grade B-Zell-Lymphom mit MYC, BCL2 und/oder BCL6 Rearrangements. Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Bei Patientinnen oder Patienten mit DLBCL nicht weiter spezifiziert (NOS) ergibt sich keine andere Vergleichstherapie. Bei Patienten oder Patientinnen mit primär mediastinalem großzelligem B-Zell-Lymphom werden durch die Erstlinienbehandlung sehr hohe Heilungsraten erzielt. Daher ist die optimale Therapie im Rezidiv oder bei Refraktärität nicht endgültig geklärt, da glücklicherweise hier die Patientenzahl sehr gering ist. Die Behandlung erfolgt analog den Empfehlungen zum refraktären/rezidivierten DLBCL. Für Patientinnen oder Patienten mit einem high-grade B-Zell-Lymphom mit MYC-, BCL2-und/oder BCL6-Rearrangements existieren bezüglich der beschriebenen Situation noch weniger Daten.

Kontaktdaten

Bundesärztekammer, Bereich Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 20.06.2022

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Kriterien, die immer berücksichtigt werden, sind der Allgemeinzustand des Patienten, Komorbiditäten und Untersuchungsergebnisse hinsichtlich der kardialen und pulmonalen Leistungsfähigkeit, um eine intensive Therapie wie die allogene Stammzelltransplantation oder die CAR-T-Zelltherapie überstehen zu können. Ist dies gegeben, sind diese beiden Verfahren die bevorzugten Therapieoptionen, die immer angestrebt werden sollten, weil sie ein kurativ es Potenzial haben.

Sollten diese intensiven Therapieformen für eine Patientin oder einen Patienten aus medizinischen, psychologischen oder anderen Gründen nicht geeignet sein, so stellen die oben angeführten Chemo-Immuntherapien die Optionen der Wahl dar.

Literatur

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

2022-B-224-z

Kontaktdaten

Fachgesellschaften:

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

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

Zusammenfassung

Das diffuse großzellige B-Zell-Lymphom (DLBCL) gehört zu den aggressiven B-Zell-Lymphomen. Die Heilungsrate der aggressiven B-Zell-Lymphome liegt bei 60 - 70%.

Standard im Rezidiv oder bei Refraktärität nach einer Zweitlinientherapie ist eine patientenindividuelle Therapie nach Maßgabe der behandelnden Ärzt*innen. Sie richtet sich vor allem nach Allgemeinzustand und Komorbidität, bisherigem Ansprechen auf die Therapie, Biologie der Erkrankung und Patientenwunsch.

Formal unterscheiden wir traditionell in Therapieoptionen in kurativer und nicht-kurativer Intention.

Optionen in kurativer Intention sind

- CAR-T-Zellen
- Hochdosistherapie mit allogener Stammzelltransplantation
- Hochdosistherapie mit autologer Stammzelltransplantation

Optionen in nicht-kurativer Intention sind

- Immunchemotherapie
- neue Arzneimittel (z. B. Antikörper-Drug-Konjugate).
- Chemotherapie

Inzwischen ist allerdings deutlich geworden, dass auch einzelne Patient*innen nach Therapie in nicht-kurativer Intention über lange Jahre progressionsfrei überleben, z. B. nach Polatuzumab Vedotin oder nach Tafasitamab / Lenalidomid.

Kontaktdaten

Fachgesellschaften:

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

Fragestellung

Der therapeutische Standard beim DLBCL nach mindestens zwei systemischen Vortherapien hat sich durch den Einsatz neuer Arzneimittel (CAR-T-Zellen, Polatuzumab Vedotin, Tafasitamab) in früheren Therapielinien geändert.

Stand des Wissens

Das diffuse großzellige B-Zell-Lymphom ist die häufigste Neoplasie des lymphatischen Systems. Es geht von reifen B-Zellen aus und führt unbehandelt rasch zum Tode. Charakteristisch sind rasch progrediente Lymphknotenvergrößerungen und/oder extranodale Manifestationen sowie Allgemeinsymptome (B-Symptomatik). Die individuelle Prognose kann mit Hilfe des Internationalen Prognostischen Index (IPI) abgeschätzt werden.

Der Therapieanspruch ist kurativ. Die Erstlinientherapie erfolgt mit 6 - 8 Zyklen des R-CHOP-Protokolls bzw. je nach Risikoprofil mit R-CHOP ähnlichen Protokollen. In frühen Stadien ist eine Reduktion der Therapiezyklen möglich. Der Stellenwert der Bestrahlung ist nicht endgültig geklärt. Weitere ungeklärte Fragen wie Prognose- oder Response-gesteuerte Therapie, der Wert intensiverer Therapieprotokolle oder die Wirksamkeit neuer Substanzen sind Gegenstand prospektiver klinischer Studien.

Die Heilungsrate von Patient*innen mit diffusem großzelligen B-Zell-Lymphom liegt bei etwa 60 - 70%.

Der aktuelle Therapiealgorithmus ist in Abbildung 1 dargestellt.

Abbildung 1: Therapiealgorithmus beim diffusen großzelligen B-Zell-Lymphom (DLBCL) [1]

Kontaktdaten

Fachgesellschaften:

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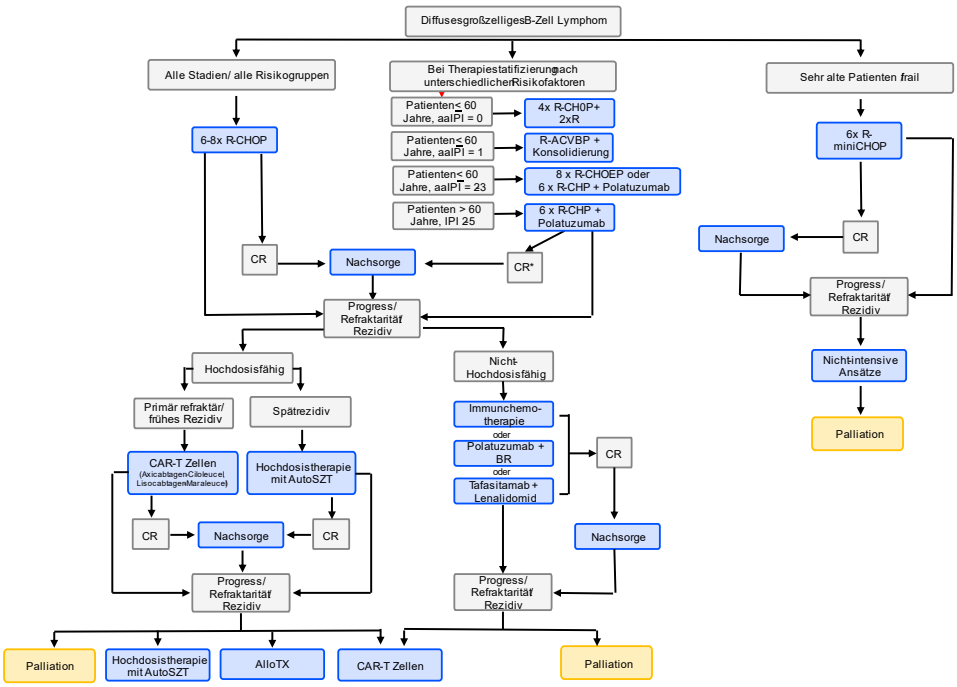

Standard im Rezidiv oder bei Refraktärität nach einer Zweitlinientherapie ist eine patientenindividuelle Therapie nach Maßgabe der behandelnden Ärzt*innen. Sie richtet sich vor allem nach Allgemeinzustand und Komorbidität, bisherigem Ansprechen auf die Therapie, Biologie der Erkrankung und Patientenwunsch. Der Therapiestandard ändert sich derzeit, nachdem der Einsatz von CAR-T-Zellen bereits im ersten Rezidiv hoch wirksam ist und empfohlen wird [2-4].

Optionen beim rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien sind:

<u>Kurativer Anspruch</u>

- CAR-T-Zellen

Kontaktdaten

Fachgesellschaften:

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

Aktuell sind von der EMA (European Medicines Agency) die CAR T-Zell-Produkte Axicabtagen Ciloleucel, Lisocabtagen Maraleucel und Tisagenlecleucel für Patient*innen mit mindestens 2 Vortherapien zugelassen [5, 6, 7]. Die Indikation besteht entsprechend den Zulassungsstudien für Patient*innen mit einem rezidivierten/refraktären diffusen großzelligen B-Zell Lymphom, einem primären mediastinalen B-Zell Lymphom bzw. einem transformierten follikulären Lymphom.

- Hochdosistherapie mit allogener Stammzelltransplantation

Jüngere Patient*innen mit chemorefraktärer Erkrankung, kurzem Intervall zwischen Primärdiagnose und Rezidiv oder Rückfall nach Hochdosistherapie, oder Patient*innen im Rezidiv oder bei Refraktärität sind potenzielle Kandidat*innen für eine allogene Stammzelltransplantation [8, 9].

- Hochdosistherapie mit autologer Stammzelltransplantation

Bisher galt als Standardtherapie für Rezidive bei jüngeren Patient*innen (unterhalb des 60. Lebensjahr), aber auch bei älteren Patient*innen ohne Therapie-limitierende Komorbiditäten in den letzten Jahrzenten eine konventionelle Salvage-Therapie gefolgt von einer Hochdosistherapie mit autologer Blutstammzelltransplantation [10]. Befriedigende Behandlungsergebnisse sind allerdings nur dann zu erwarten, wenn das Rezidiv auf die konventionell dosierte Induktionstherapie anspricht. Bei einem Intervall zwischen Primärdiagnose und Rezidiv < 12 Monate ist dies nur selten der Fall. Als Induktionstherapie erwiesen sich die R-GDP, R-DHAP- bzw. R-ICE-Protokolle als gleichwertig [11, 12]. Für die Hochdosistherapie wird meist das BEAM-Protokoll verwendet [11]. Eine Erhaltungstherapie mit Rituximab ist nicht indiziert. Die Hochdosistherapie bleibt eine Option nach einer CAR-T-Zelltherapie.

<u>Nicht-kurativer Anspruch</u>

Bei Patient*innen, die aufgrund ihres Alters oder ihrer Komorbidität für eine autologe oder allogene Blutstammzelltransplantation bzw. eine CAR T-Zell-Therapie nicht in Frage kommen, ist das Behandlungsziel häufig palliativ. Ein kurativ Therapiekonzept erscheint möglich, wenn das Intervall zwischen vorheriger Therapie und dem Rezidiv lang ist.

- Immunchemotherapie

Kontaktdaten

Fachgesellschaften:

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

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Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

Neben dem R-GemOx-Regime [13] können auch intensivere Chemotherapie-Regime wie R-DHAP- oder R-ICE-Protokoll eingesetzt werden.

- neue Arzneimittel (z. B. Antikörper-Drug-Konjugate)

Eine wirksame Kombination besteht aus Rituximab, Bendamustin und dem Antikörper-Wirkstoff-Konjugat Polatuzumab-Vedotin (Pola-BR). Diese Kombination ist bei Patient*innen im 1. Rezidiv eines diffusen großzelligen B-Zell-Lymphoms, die nicht für eine hämatopoetische Stammzelltransplantation in Frage kommen, zugelassen. Die Zulassungsstudie für Pola-BR zeigte im Vergleich zu Rituximab und Bendamustin eine signifikante Verbesserung der Ansprechraten, des progressionsfreien und des Gesamtüberlebens [14]. Eine weitere wirksame und zugelassene, neue Option besteht aus dem Anti-CD19-Antikörper Tafasitamab in Kombination mit Lenalidomid [15, 16].

- Chemotherapie

Für mehrfach rezidivierte aggressive B-Zell-Lymphome stehen auch das Anthracendion-Derivat Pixantron oder Bendamustin zur Verfügung [17, 18].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind in einer patientenindividuellen Therapie nach Maßgabe der behandelnden Ärzt*innen enthalten.

Literatur / Referenzen

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Kontaktdaten

Fachgesellschaften:

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

2. Locke FL, Miklos DB, Jacobson C et al.: Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med 386:640-654, 2022. DOI: 10.1056/NEJMoa2116133
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Kontaktdaten

Fachgesellschaften:

DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie

Indikation gemäß Beratungsantrag

Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL) nach zwei oder mehr systemischen Vortherapien

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