Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2023-B-166 Enfortumab Vedotin

Stand: August 2024

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

Enfortumab Vedotin
[zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms; Erstlinientherapie]

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“ • Die Liste bezieht sich nur auf die Erstlinienbehandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Pembrolizumab (Urothelkarzinom): Beschluss vom 16. September 2021 • Atezolizumab (Urothelkarzinom): Beschluss vom 16. März 2018 und Änderungsbeschluss vom 2. August 2018; Beschluss vom 20. Juni 2019 und Änderungsbeschluss vom 6. April 2023 • Avelumab (Urothelkarzinom): Beschluss vom 19. August 2021 Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI (Off-Label-Use): • Carboplatin in Kombination mit Gemcitabin zur Behandlung von Patientinnen und Patienten mit inoperablem lokal fortgeschrittenem oder metastasiertem Urothelkarzinom, wenn eine Cisplatin-Therapie nicht infrage kommt (Beschluss vom 20. Mai 2021)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen	*Siehe „systematische Literaturrecherche“*

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

Enfortumab Vedotin
[zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms; Erstlinientherapie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Therapie im Anwendungsgebiet gehören.	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Enfortumab Vedotin L01FX13 PADCEV	<u>Anwendungsgebiet laut Positive Opinion:</u> Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.
Cisplatin L01XA01 Generisch	Cisplatin wird angewendet zur Behandlung des: • fortgeschrittenen oder metastasierten Harnblasenkarzinoms • […]
Doxorubicin L01DB01 Generisch	• Systemische Therapie des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms • […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Epirubicin L01DB03 Generisch	Bei intravesikaler Anwendung hat sich Epirubicin bei der Behandlung folgender Erkrankungen als wirksam erwiesen: • papilläres Übergangszellkarzinom der Harnblase • Carcinoma in situ der Harnblase
Methotrexat L01BA01 Generisch	Methotrexat 25 mg/ml Injektionslösung wird angewendet bei: • Harnblasenkarzinomen - in Kombination mit anderen zytotoxischen Arzneimitteln • […]
Gemcitabin L01BC05 Generisch	• In Kombination mit Cisplatin zur Behandlung des lokal fortgeschrittenen oder metastasierten Harnblasenkarzinoms.
Pembrolizumab L01FF02 Keytruda	Pembrolizumab ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden Urothelkarzinoms bei Erwachsenen, die nicht für eine Cisplatin-basierte Therapie geeignet sind und deren Tumoren PD-L1 mit einem kombinierten positiven Score (CPS) ≥ 10 exprimieren, angezeigt. […]
Atezolizumab L01FF05 Tecentriq	Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten Urothelkarzinoms (UC) • die für eine Behandlung mit Cisplatin als ungeeignet angesehen werden, und deren Tumoren eine PD-L1-Expression ≥ 5 % aufweisen. • […]
Avelumab L01FF04 Bavencio	Als Monotherapie in der Erstlinien-Erhaltungstherapie bei erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinom (urothelial carcinoma, UC) angewendet, die nach einer platinbasierten Chemotherapie progressionsfrei sind.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-166 (Enfortumab Vedotin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	1. August 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AMUC	Advanced or metastatic urothelial carcinoma
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CIS	Cisplatin
G-BA	Gemeinsamer Bundesausschuss
GC	Gemcitabine plus cisplatin
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MVAC	Methotrexate, vinblastine, adriamycin, and cisplatin
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
(UT)UC	(Upper tract) urothelial carcinoma
G-CSF	Granulocyte colony-stimulating factor
PD-L1	Programmed death ligand 1
PCG	Paclitaxel, cisplatin, gemcitabine
EAU	European Association of Urology

1 Indikation

Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinom.

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

2 Systematische Recherche

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

Die Erstrecherche wurde am 24.06.2021 abgeschlossen, die folgenden am 12.07.2022 und 30.01.2023. 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 1411 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

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Chen HL et al., 2021 [1].

Immune checkpoints inhibitors and chemotherapy as first-line treatment for metastatic urothelial carcinoma: a network meta-analysis of randomized phase III clinical trials.

Fragestellung

to assess different immune checkpoints inhibitors (ICIs) regimens in the efficacy and safety for frontline treatments in mUC patients.

Methodik

Population:

- patients with mUC

Intervention/Komparator:

- NMA: different ICIs

Endpunkte:

- overall survival (OS), progression of free survival (PFS), objective response rate (ORR), and grade 3–5 adverse events

Recherche/Suchzeitraum:

- Medline/PubMed, Embase, Cochrane library (CENTRAL and CDSR), and Clinical-Trials.gov up to 15 October 2020

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 published studies retrieved from three completed RCTs

Charakteristika der Population:

Table 1. Characteristics of the included studies.

Trial Name	Year	NCT Number	Phase	ICI-Based Treatment	ICI Category	Design	Stage	Median Age	Males (%)	Site of Metastatic Disease (%)	Treatment Arm (Patient Number)
IMvigor130	2020	NCT02807636	3	atezolizumab	PD-L1 inhibitors	three arms open-label	advanced or metastatic	67–69	75–77	Lymph node only (17.89%) Visceral metastases (79.96%)	1. atezolizumab (360) 2. atezolizumab + platinum-based CTX (451) 3. platinum-based CTX (400)
DANUBE	2020	NCT02516241	3	durvalumab tremelimumab	PD-L1 inhibitors CTLA4 inhibitors	three arms open-label	advanced or metastatic	67–68	72–80	Lymph node only (20.45%) Visceral metastases (79.36%)	1. durvalumab (346) 2. durvalumab + tremelimumab (342) 3. platinum-based CTX (344)
KEYNOTE-361	2020	NCT02853305	3	pembrolizumab	PD-1 inhibitors	three arms open-label	advanced or metastatic	68–69	74.3–77.5	Lymph node only (23.66%) Visceral metastases (74.26%)	1. pembrolizumab (307) 2. pembrolizumab + platinum-based CTX (351) 3. platinum-based CTX (352)

Qualität der Studien:

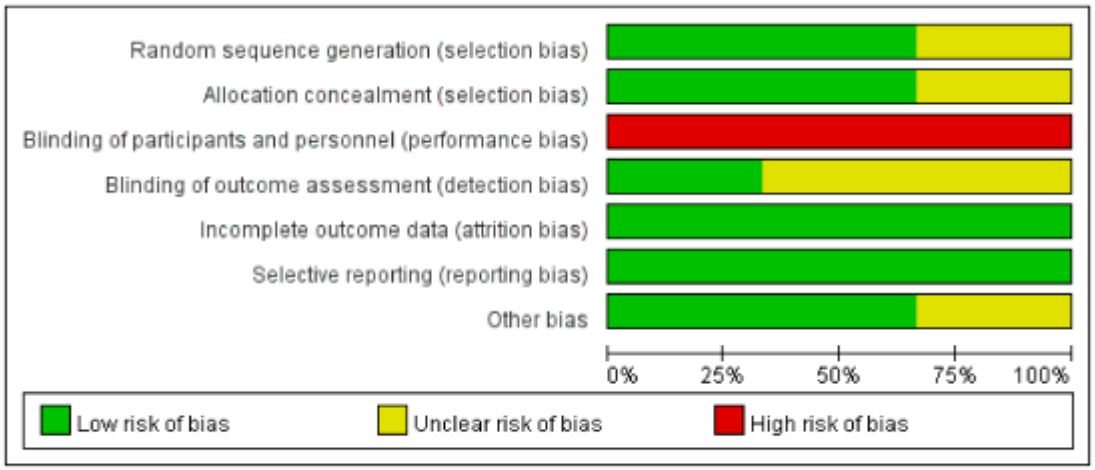


Figure A1. Quality assessment by the risk of bias (ROB) tool.

Studienergebnisse:

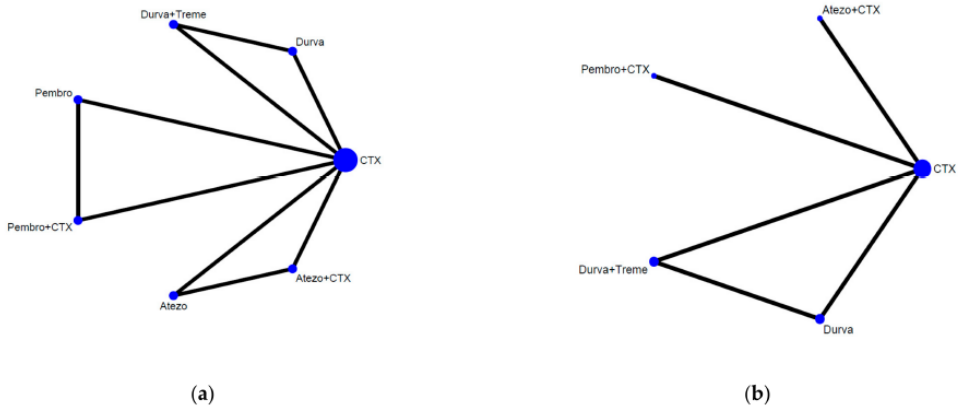


Figure 2. Network constructions for comparison in overall survival (OS), progression of free survival (PFS), objective response rate (ORR), and grade 3–5 adverse events (AEs). (a) Network constructions for comparison in OS (hazard ratio (HR)), ORR, grade 3-5 AEs. (b) Network constructions for comparison in PFS (HR).

- The survival benefit of a single ICI was non-inferiority to chemotherapy (CTX). Although no superior effects were indicated, combination therapy (either ICIs plus CTX or ICIs plus ICIs) presented better OS compared with CTX alone.
- In terms of PFS, combination therapy produced a noticeable benefit over CTX.
- Regarding the SUCRA ranking, atezolizumab plus CTX was associated with the best ranking for OS and pembrolizumab plus CTX was the best in PFS.
- In terms of safety, a single ICI had better safety profile than CTX and combination therapy had a similar risk of grade 3–5 adverse events with CTX.

Anmerkung/Fazit der Autoren

From this NMA focusing on the first-line treatment of mUC patients, combination therapy (either ICIs plus CTX or ICIs plus ICIs) had a higher priority in terms of OS upon the ranking analysis. Concerning monotherapy, ICIs are not inferior to CTX in terms of OS. The benefit of combination therapy is presented regardless of gender and age upon the subgroup analysis. In view of the adverse effect, ICIs are very tolerable, and combination therapy did not lead to a higher incidence of grade 3–5 AEs when compared with CTX.

Mori K et al., 2021 [3].

First-line immune-checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: a systematic review and meta-analysis.

Fragestellung

to assess the role of ICIs alone or in combination as first-line treatment in chemotherapy-eligible patients with mUC.

Methodik

Population:

- chemotherapy-eligible patients with mUC

Intervention/Komparator:

- first-line systemic therapy

Endpunkte:

- overall survival (OS), progression-free survival (PFS), objective response rates (ORRs), complete response rates (CRRs), durations of response (DORs) and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, Web of Science and Scopus were searched to identify reports published up to November 2020

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Three studies

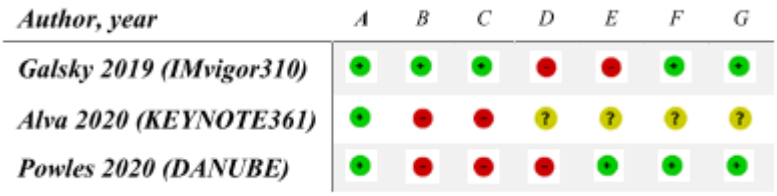
Charakteristika der Population:

Table 1
Study demographics.

Study	IMvigor130			DANUBE			KEYNOTE361		
Year	2019			2020			2020		
Compound	Atezo Chemo	Atezo	Chemo	Durva Treme	Durva	Chemo	Pembro Chemo	Pembro	Chemo
Number	451	362	400	342	346	344	351	307	352
Age	69 (62–75)	67 (62–74)	67 (61–73)	68 (60–73)	67 (60–73)	68 (60–73)	69 (41–91)	68 (29–89)	69 (36–90)
Male	75%	77%	75%	75%	72%	80%	78%	74%	74%
ECOG PS 2	13%	9%	10%	0%	0%	0%	7%	8%	6%
Primary tumour (lower tract)	71%	75%	75%	78%	82%	75%	82%	79%	77%
Disease status (metastatic)	89%	88%	92%	96%	97%	94%	NR	NR	NR
Lymph node only	18%	19%	17%	21%	18%	22%	23%	21%	27%
Visceral meta	57%	56%	60%	78%	82%	77%	74%	78%	72%
High PD-L1	24%	24%	23%	60%	60%	60%	45%	52%	45%
Antibodies	SP142			SP263			22c3		
Platform	Ventana			Ventana			Dako		
Cell type	IC			IC/TC			TC		
Cut-off	≧5%			≧25%			CPS≧10		
Cisplatin eligible	42%	47%	44%	57%	57%	56%	NR	NR	NR
Chemotherapy (Cisplatin)	30%	37%	34%	NR	NR	NR	46%	45%	46%
Subsequent therapy	26%	40%	41%	45%	47%	54%	35%	41%	61%
Subsequent ICI therapy	5%	2%	20%	3%	5%	32%	7%	5%	48%
Follow up	11.8 months			41.2 months			NR		

Abbreviation: Atezo (Atezolizumab), Chemo (Chemotherapy), CPS (Combines positive score), Durva (Durvalumab), IC (Immune cell), ICI (Immune checkpoint inhibitor), NR (Not reported), PD-L1 (Programmed death ligand 1), Pembro (Pembrolizumab), PS (Performance status), TC (Tumour cell), Treme (Tremelimumab).

Qualität der Studien:



Studienergebnisse:

- ICI combination therapy was associated with significantly better OS and PFS, higher CRR and longer DOR than chemotherapy alone (hazard ratio [HR]: 0.85, 95% confidence interval [CI]: 0.76-0.94, P Z 0.002; HR: 0.80, 95% CI: 0.71-0.90, P Z 0.0002; odds ratio [OR]: 1.48, 95% CI: 1.12-1.96, P Z 0.006; and mean difference: 1.39, 95% CI: 0.31-2.46, P Z 0.01, respectively).
- ICI-chemotherapy combination therapy was also associated with significantly better OS and PFS, higher ORR and CRR and longer DOR than chemotherapy alone. Although OS and PFS benefits of ICI combination therapy were larger in patients with high expression of programmed death-ligand 1 (PD-L1), PD-L1 low expression patients also had a benefit; HR for OS (high PD-L1: HR 0.79 versus low PD-L1: HR 0.89) and PFS (high PD-L1: HR 0.74 versus low PD-L1: HR 0.82).
- ICI monotherapy was not associated with better oncological outcomes but was associated with better safety outcomes than chemotherapy alone.

Anmerkung/Fazit der Autoren

Our analysis indicates that first-line ICI combination therapies confer a superior oncological benefit compared with standard chemotherapy in chemotherapy-eligible mUC patients. This superiority over chemotherapy remained intact even in our analyses focused on ICI-chemotherapy combination studies alone. In contrast, ICI monotherapy does not seem as an attractive alternative to chemotherapy alone in these patients when it comes to efficacy. However, ICI monotherapy offers a better safety profile than chemotherapy alone. Moreover, PD-L1 status alone is not a sufficiently robust, reliable and reproducible biomarker to guide treatment decision-making in chemotherapy eligible mUC. These findings may be valuable in determining personalized treatment strategies for chemotherapy-eligible mUC patients. However, the conclusions drawn from this study should be interpreted with caution, given that there is the heterogeneity of the population of interest, risk of bias and the nature of the RCTs evaluated whose data remain immature or unpublished.

Kommentare zum Review

- Es liegt ein weiterer SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Li H et al., 2022 [2]

Qu HC et al., 2019 [6].

Efficacy and safety of chemotherapy regimens in advanced or metastatic bladder and urothelial carcinomas: an updated network meta-analysis.

Fragestellung

"We aimed to comprehensively compare all possible regimens with GC or MVAC in randomized controlled trials (RCTs) by network meta-analysis."

Methodik

Population:

- Advanced or metastatic urothelial carcinoma (AMUC)

Intervention/ Komparator:

- Methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) or gemcitabine plus cisplatin (GC) with other strategies

Endpunkte:

- Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR)

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library up to 10 April 2019

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias & GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

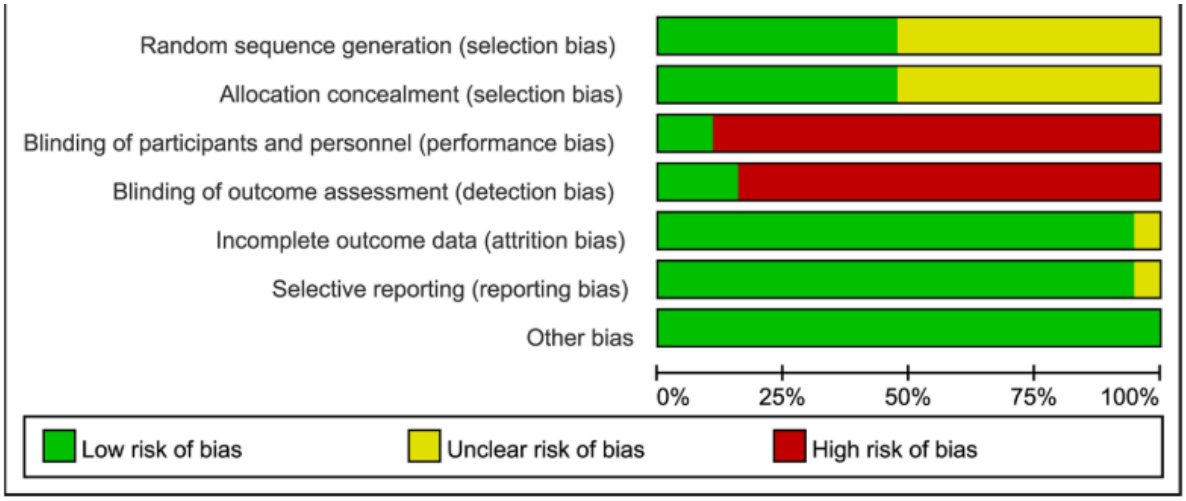
- A total of 19 trials that assessed 3,363 AMUC patients

Charakteristika der Population:

- The median age was 60–70 years old.
- Three articles included only advanced bladder cancer patients

Qualität der Studien:

- All included studies were of RCT design, but in some studies, the generation of random sequences and random masking were not clearly described. Three studies were blinded (Bellmunt et al., 2012; Krege et al., 2014; Bellmunt et al., 2017). Because the main evaluation results are objective, the quality of the research was generally acceptable.



Studienergebnisse:

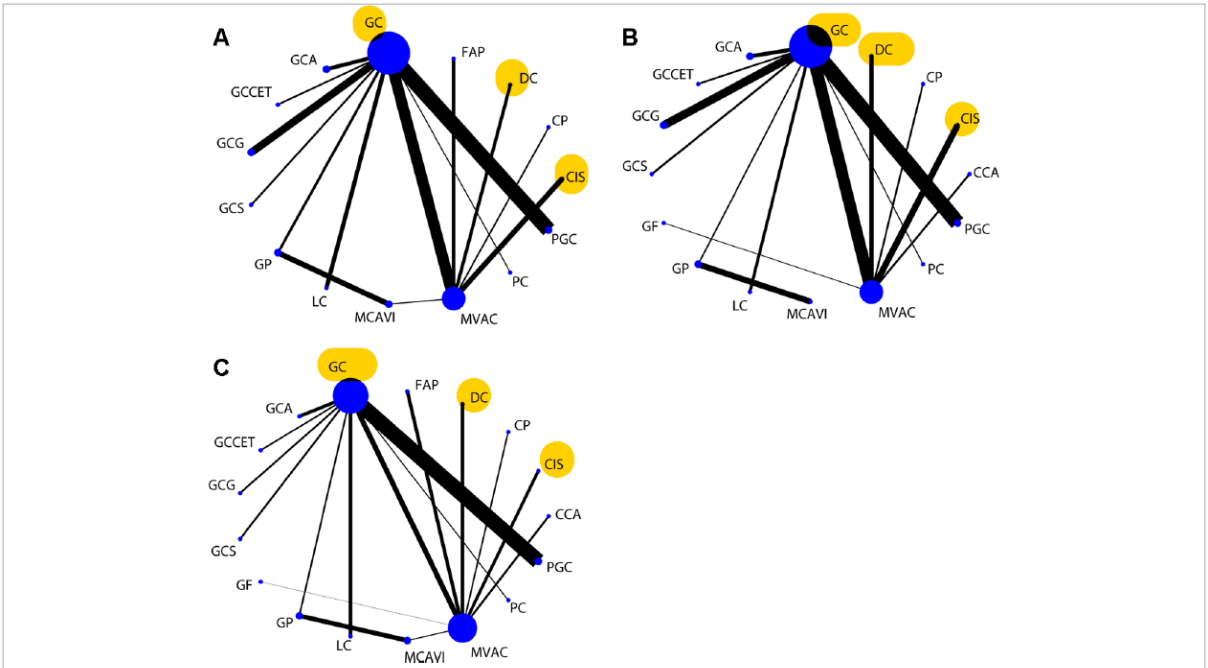


FIGURE 3 | Network of comparisons for the treatment strategies included in the analyses. **(A)** PFS; **(B)** OS; **(C)** ORR. Strategy abbreviations are listed in **Table 1**.

- The inconsistency analysis showed that no global (p = 0.8229) or local inconsistencies (inconsistency factor: 0.19; 95% CI: 0.00, 1.84) were detected.
- PFS:

Supplementary table 2. The PFS results of chemotherapy strategies according to their relative effect and reliable quality.

Interventions	Direct comparisons		Indirect comparisons		Network comparisons	
	LogHR(95%CIs)	Quality	LogHR(95%CIs)	Quality	LogHR(95%CIs)	Quality
[…]						
GC vs.						
FAP			-0.11 (-0.48,0.26)	Moderate*	-0.11 (-0.48,0.26)	Moderate*
DC			**-0.42 (-0.80,-0.05)**	**Moderate***	**-0.42 (-0.80,-0.05)**	**Moderate***
CP			-0.13 (-0.64,0.38)	Low*‡	-0.13 (-0.64,0.38)	Low*‡
CIS			**-0.66 (-0.98,-0.34)**	**Moderate***	**-0.66 (-0.98,-0.34)**	**Moderate***
GCCET	-0.07 (-0.53,0.39)	Low*‡	NA	NA	-0.07 (-0.53,0.39)	Low*‡
DC vs.						
CP			0.29 (-0.29,0.88)	Low*‡	0.29 (-0.29,0.88)	Low*‡
CIS			-0.24 (-0.66,0.19)	Low*‡	-0.24 (-0.66,0.19)	Low*‡
GCCET			0.36 (-0.24,0.95)	Low*‡	0.36 (-0.24,0.95)	Low*‡

Abbreviations: CIs: confidence intervals; LogOR: logarithm hazard ratio; NA: not available.

Bold means statistic difference (p<0.05).

*: Study limitation; †: Large-scale effect; ‡: Imprecision; #: Incoherence.

- OS:

Supplementary table 3. The OS results of chemotherapy strategies according to their relative effect and reliable quality.

Interventions		Direct comparisons		Indirect comparisons		Network comparisons	
		LogHR(95%CIs)	Quality	LogHR(95%CIs)	Quality	LogHR(95%CIs)	Quality
[…]							
GC vs.							
	GCA	0.13 (-0.20,0.45)	High	NA	NA	0.13 (-0.20,0.45)	high
	GF			0.15 (-0.66,0.96)	Low*‡	0.15 (-0.66,0.96)	Low*‡
	DC			-0.35 (-0.71,0.02)	Moderate*	-0.35 (-0.71,0.02)	Moderate*
	CP			-0.09 (-0.60,0.42)	Low*‡	-0.09 (-0.60,0.42)	Low*‡
	CIS			**-0.44 (-0.76,-0.12)**	**Moderate***	**-0.44 (-0.76,-0.12)**	**Moderate***
DC vs.							
	CP			0.26 (-0.31,0.82)	Low*‡	0.26 (-0.31,0.82)	Low*‡
	CIS			-0.09 (-0.50,0.31)	Low*‡	-0.09 (-0.50,0.31)	Low*‡

Abbreviations: CIs: confidence intervals; LogOR: logarithm hazard ratio; NA: not available.

Bold means statistic difference (p<0.05).

*: Study limitation; †: Large-scale effect; ‡: Imprecision; #: Incoherence.

- ORR:

Supplementary table 4. The ORR results of chemotherapy strategies according to their relative effect and reliable quality.

Interventions		Direct comparisons		Indirect comparisons		Network comparisons	
		logOR(95%CIs)	Quality	logOR(95%CIs)	Quality	logOR(95%CIs)	Quality
[…]							
GC vs.							
	GF			**4.96 (2.42,7.51)**	Low*‡	**4.96 (2.42,7.51)**	Low*‡
	FAP			**0.87 (0.09,1.65)**	Low*‡	**0.87 (0.09,1.65)**	Low*‡
	DC			**0.86 (0.09,1.64)**	Low*‡	**0.86 (0.09,1.64)**	Low*‡
	CP			0.33 (-0.72,1.39)	Low*‡	0.33 (-0.72,1.39)	Low*‡
	CIS			**1.68 (0.86,2.50)**	Low*‡	**1.68 (0.86,2.50)**	Low*‡
DC vs.							
	CP			-0.53 (-1.65,0.58)	Low*‡	-0.53 (-1.65,0.58)	Low*‡
	CIS			0.82 (-0.08,1.71)	Low*‡	0.82 (-0.08,1.71)	Low*‡

Abbreviations: CIs: confidence intervals; LogOR: logarithm hazard ratio; NA: not available.

Bold means statistic difference (p<0.05).

*: Study limitation; †: Large-scale effect; ‡: Imprecision; #: Incoherence.

- AE:

- The cluster results of safety outcomes and SAE (grade> = 3) included analyses of neutropenia, anemia, thrombocytopenia, infection, mucositis, and nausea/vomiting, which are frequently reported. The cluster analysis showed that regimens such as cisplatin, MCAVI, CP, LC, and DC had fewer SAEs but were also less effective.
- The cytotoxic drugs that have a weak effect on cancer cells may also have a weaker effect on normal cells.
- GC-related treatment strategies, such as GC, GCCET, GCS, GCA, and gemcitabine, cisplatin, and gefitinib (GCG), had similar SAE clusters

Anmerkung/Fazit der Autoren

In our analysis, PGC was superior to MVAC and GC in only the ORR results and superior to GC in the OS and PFS results but was not significantly different from MVAC. More individualized therapies with targeted drugs need to be studied.

Anmerkungen zur Publikation

- Zugelassene Wirkstoff(kombinationen) sind gelb markiert: Gemcitabin + Cisplatin (GC), Doxorubicin + Cisplatin (DC), Cisplatin (CIS).
- Keine Eingrenzung auf Erst-/Zweitlinie.
- Relevanz von ORR und PFS im Anwendungsgebiet unklar.

3.3 Leitlinien

Rouprêt M et al., 2022 [7,8]

European Association of Urology (EAU)

EAU guidelines on upper urinary tract urothelial carcinoma.

Zielsetzung/Fragestellung

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of upper urinary tract urothelial carcinoma (UTUC).

Methodik

<u>Grundlage der Leitlinie</u>

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Verfahren zur Konsensfindung nicht beschrieben, externes Begutachtungsverfahren (vor Veröffentlichung im Jahr 2016) dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum des Updates:

- The search was restricted to articles published between May 29th 2020 and June 8th 2021. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
- For the 2023 UTUC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between June 8th 2021 and May 4th 2022.

LoE/GoR

- […] the overall quality of the evidence which exists for the recommendation references used in this text are graded according to the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence. For the Disease Management […] chapters a system modified from the 2009 CEBM LEs has been used.
- The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between diserable and undiserable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Recommendations 7.2.Metastatic disease

7.3 Metastatic disease

7.3.1 ***Clinical loco-regional lymph node metastases***

Evidence is lacking regarding the optimal management of clinical node-positive disease. Patients with clinically N+ UTUC should be offered first-line chemotherapy. In patients whose cancer responds or who have stable disease, maintenance avelumab can be offered [276]. Depending on the extent of the nodal disease (i.e., cN1/N2) surgical resection with LN dissection can be discussed after initial systemic therapy. In patients whose cancer progress, second-line treatment can be offered, similar to metastatic disease [277, 278].

7.3.2 ***Distant metastases***

7.3.2.1 *Systemic treatments*

7.3.2.1.1 First-line setting

7.3.2.1.1.1 Patients fit for cisplatin-based combination chemotherapy

Upper tract UC and urothelial BC both respond to systemic platinum-based chemotherapy. A retrospective analysis of three RCTs showed that primary tumour location in the lower- or upper urinary tract had no impact on progression-free survival (PFS) or OS in patients with locally-advanced or metastatic UC treated with platinum-based combination chemotherapy [279]. Therefore, cisplatin-containing combination chemotherapy is the standard treatment for advanced or metastatic UTUC [2]. A number of cisplatin-containing chemotherapy regimens have proven efficacy although gemcitabine and cisplatin are the most widely used. The use of cisplatin-based chemotherapy is widely considered in patients with eGFR > 45 mL/min [279].

The efficacy of immunotherapy using PD1 or PD-L1 inhibitors has been evaluated in the first-line setting for the treatment of cisplatin/carboplatin-fit patients with metastatic UC, including those with UTUC [280]. First-line immune checkpoint inhibitors or the combination of platinum-based chemotherapy with immune checkpoint inhibitors have not resulted in positive significant survival advantages and are not currently recommended [281-283].

7.3.2.1.1.2 Patients unfit for cisplatin-based combination chemotherapy

Carboplatin-based chemotherapy is recommended in patients unfit for cisplatin [2]. Carboplatin with gemcitabine is the preferred regimen [284], irrespective of PDL-1 status. In a recent critical re-analysis of RCTs comparing OS after cisplatin vs. carboplatin-based regimens in advanced UC, cisplatin confered a minor OS benefit compared to carboplatin [285].

7.3.2.1.1.3 Maintenance therapy after first-line platinum-based chemotherapy

Maintenance avelumab is recommended in patients with complete/partial response or stable disease after 4–6 cycles of platinum-based chemotherapy. Data from a phase III RCT showed that the use of avelumab maintenance therapy after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin (started within 10 weeks of completion of first-line platinum-based chemotherapy) significantly prolonged OS as compared to best supportive care alone in those patients with advanced or metastatic UC who did not progress during, or responded to, first-line chemotherapy (HR: 0.69; 95% CI: 0.56–0.86) [276, 286]. An increase in median OS from 14 to 21 months was observed with avelumab. Although no subgroup analysis based on tumour location was available in this study, almost 30% of the included patients had UTUC. Similarly, in a phase II study comprising 108 patients with metastatic UC achieving at least stable disease on first-line platinum-based chemotherapy, maintenance pembrolizumab improved PFS compared to placebo (5.4 vs. 3.0 months) [287].

7.3.2.1.1.4 Patients unfit for platinum-based combination chemotherapy

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible/ fit for platinum-based chemotherapy. In a single-arm phase II trial (n = 370) of cisplatin-ineligible UC, pembrolizumab monotherapy was associated with an objective response rate of 26% in 69 metastatic UTUC patients [288]. In the overall cohort, a PD-L1 expression of 10% was associated with a greater response rate to pembrolizumab. Treatment-related toxicity was in line with previous studies. In a single-arm phase II trial (n = 119) of cisplatin-ineligible UC, atezolizumab monotherapy was associated with an objective response rate of 39% in 33 (28%) metastatic UTUC patients [289]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies [282].

7.3.3 Summary of evidence and recommendations for the treatment of metastatic UTUC

Summary of evidence	**LE**
Cisplatin-based combination chemotherapy can improve median survival.	2
Cisplatin-containing combination chemotherapy is the standard of care in advanced or metastatic patients fit enough to tolerate cisplatin.	1b
Carboplatin-based combination chemotherapy offers a survival benefit in cisplatin unfit patients.	1b
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus either cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients whose disease has progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a

PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial, but use of atezolizumab is restricted to PD-L1 positive patients.	2a
Erdafitinib was associated with radiological response in platinum-refractory patients with locally-advanced or metastatic UC and *FGFR* DNA genomic alterations (*FGFR2/3* mutations or *FGFR3* fusions).	2a
Enfortumab vedotin was associated with OS benefit in patients who had previously received platinum-containing chemotherapy and experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	1b
Palliative nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients.	4

Recommendations	**Strength rating**
First-line treatment for platinum-eligible patients	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin/carboplatin.	Strong
First-line treatment in patients ineligible for cisplatin or carboplatin	
Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak

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Witjes JA et al., 2023 [9,10].

European Association of Urology (EAU)

EAU guidelines on muscle-invasive and metastatic bladder cancer.

Zielsetzung/Fragestellung

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Methodik

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, keine Einbeziehung von Patientenvertretungen,
- 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.

Recherche/Suchzeitraum des 2023 Updates:

- For the 2023 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between June 11th, 2021 and May 4th 2022.

LoE/ GoR

- […] classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence.
- The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between diserable and undiserable consequences of alternative management strategies, the quality of the

evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Recommendations

7.7 Metastatic disease

7.7.1 Introduction

The treatment of metastatic UC had remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations demonstrating an OS benefit. In the past few years this long-standing paradigm has been challenged by several large studies investigating the benefit of immunotherapy using checkpoint inhibitors. Moreover, novel compounds including both targeted therapy and antibody-drug conjugates have been successfully tested and approved in later treatment lines.

7.7.2 First-line systemic therapy for metastatic disease

In general, patients with untreated metastatic UC can be divided into three broad categories: fit for cisplatin-based chemotherapy, fit for carboplatin-based chemotherapy (but unfit for cisplatin) and unfit for any platinum-based chemotherapy.

Definitions: 'Fit for cisplatin, fit for carboplatin, unfit for any platinum-based chemotherapy'

An international survey among BC experts [469] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria must be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric hearing loss; grade ≥ 2 peripheral neuropathy or New York Heart Association (NYHA) class III heart failure [470]. Around 50% of patients with BC are not eligible for cisplatin-based chemotherapy [470]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes (^{99}mTc DTPA or ^{51}Cr-EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a lower GFR (40–60 mL/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [468, 471, 472]. However, no prospective RCT has compared split-dose cisplatin with conventional dosing.

Most patients that are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. However, some patients are deemed unfit for any platinum-based chemotherapy, i.e. both cisplatin and carboplatin. Patient are unfit for any platinum-based chemotherapy in case of PS > 2, GFR < 30 mL/min or the combination of PS 2 and GFR < 60 mL/min since the outcome in this patient population is poor regardless of platinum-based treatment or not [473]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy. Definitions of platinum-eligibility for first-line treatment of metastatic UC are summarised in Table 7.2.

Table 7.2: Definitions of platinum-eligibility for first-line treatment of metastatic urothelial carcinoma

Platinum-eligible		Platinum-ineligible
Cisplatin-eligible	**Carboplatin-eligible**	
ECOG PS 0-1 *and*	ECOG PS 2 *or* GFR 30–60 mL/min	Any of the following:
GFR > 50–60 mL/min *and*	or not fulfilling other cisplatin-eligibility criteria	GFR < 30 mL/min
Audiometric hearing loss grade < 2 *and*		ECOG PS > 2
Peripheral neuropathy grade < 2 *and*		ECOG PS 2 *and* GFR < 60 mL/min
Cardiac insufficiency NYHA class < III		Comorbidites > Grade 2

ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; NYHA = New York Heart Association; PS = performance status.

7.7.2.1 *First-line chemotherapy in patients fit for cisplatin*

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s demonstrating an OS of 12 to 14 months in different series (for a review see [474]). Methotrexate, vinblastine, adriamycin plus cisplatin and GC achieved survival of 14.8 and 13.8 months, respectively [475]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC [204] compared to standard MVAC has resulted in GC becoming the standard regimen.

Dose-dense MVAC combined with granulocyte colony-stimulating factor (G-CSF) is less toxic and more efficacious than standard MVAC in terms of, complete response (CR), and 2-year OS. However, there is no significant difference in median survival between the two regimens [476, 477]. Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the intention-to-treat (ITT) population of a phase III RCT, comparing PCG to GC [478]. Similarly, the addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [479].

The disease sites have an impact on long-term survival. In LN-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [475]. In the trials with long-term follow-up approximately 10-15% of patients with metastatic UC are alive at 5 years and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [475, 477].

Carboplatin-containing chemotherapy is not considered to be equivalent to cisplatin-based combinations, and should not be considered interchangeable or standard in patients fit for cisplatin. A comparative analysis of four randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy demonstrated lower CR rates and shorter OS for the carboplatin arms [480]. Recently, a retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients in order to maintain benefit [481].

7.7.2.2 *First-line chemotherapy in patients fit for carboplatin (but unfit for cisplatin)*

Up to 50% of patients are not fit for cisplatin-containing chemotherapy but most may be candidates for carboplatin [470]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared two carboplatin-containing regimens (methotrexate/carboplatin/vinblastine [M-CAVI] and gemcitabine/carboplatin [GemCarbo]) in patients unfit for cisplatin. The EORTC definitions for eligibility were GFR < 60 mL/min and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI, respectively [473]. Based on these results the combination of carboplatin and gemcitabine should be considered a standard of care in this patient group.

Combinations of gemcitabine and paclitaxel have been studied as first-line treatment and produced response rates between 38% and 60% but has never been tested in RCTs [482-484]. A randomised phase II trial assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine/gemcitabine vs. vinflunine/carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination of vinflunine/gemcitabine [485]. Non-platinum combination chemotherapy is nevertheless not recommended for first-line use in platinum-eligible patients.

The use of single-agent chemotherapy has been associated with varying response rates. Responses with single agents are usually short, complete responses are rare, and no long-term DFS/OS has been reported. It is not recommended for first-line treatment of metastatic UC.

7.7.2.3 Integration of immunotherapy in the first-line chemotherapy treatment of patients fit for platinum (cisplatin or carboplatin)

7.7.2.3.1 Immunotherapy combination approaches

In 2020, the results of three phase III trials have been published investigating the use of immunotherapy in the first-line setting for platinum-eligible patients. The first trial to report was IMvigor130 investigating the combination of the PD-L1 inhibitor atezolizumab plus platinum-gemcitabine chemotherapy vs. chemotherapy plus placebo vs. atezolizumab alone [486]. The primary endpoint of PFS benefit for the combination vs. chemotherapy alone in the ITT group was reached (8.2 months vs. 6.3 months [HR: 0.82, 95% CI: 0.70–0.96; one-sided, p = 0.007]) while OS was not significant at the interim analysis after a median follow-up of 11.8 months. The small PFS benefit in the absence of an OS benefit has raised questions of its clinical significance. Due to the sequential testing design, the comparison of chemotherapy vs. atezolizumab alone has not yet been formally performed.

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine vs. chemotherapy plus placebo vs. pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy vs. chemotherapy plus placebo in the ITT population showed no benefit for the combination [487].

DANUBE compared the immunotherapy combination (IO-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [488]. The co-primary endpoint of improved OS for the IO-IO combination vs. chemotherapy was not reached in the ITT group nor was the OS improved for durvalumab monotherapy vs. chemotherapy in the PD-L1-positive population.

In conclusion, these three trials do not support the use of combination of PD-1/L1 checkpoint inhibitors plus chemotherapy or the IO-IO combination as first-line treatment.

7.7.2.3.2 Use of first-line single-agent immunotherapy in patients unfit for cisplatinum-based chemotherapy

Based on the results of two single-arm phase II trials [489, 490] the checkpoint inhibitors pembrolizumab and atezolizumab have been approved by the U.S. FDA and the EMA for first-line treatment in cisplatin-unfit patients in case of positive PD-L1 status. PD-L1 positivity for use of pembrolizumab is defined by immunohistochemistry as a CPS of ≥ 10 using the Dako 22C33 platform and for atezolizumab as positivity of ≥ 5% tumour-infiltrating immune cells using Ventana SP142.

Pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [489]. Atezolizumab was evaluated in the same patient population in a phase II trial (n = 119) showing an ORR of 23% with 9% of patients achieving CR [490].

The trials IMvigor 130, Keynote 361 and DANUBE all included an experimental arm with immunotherapy alone using atezolizumab, pembrolizumab and durvalumab, respectively [486-488]. No benefit in terms of PFS or OS for the use of single-agent immunotherapy compared to platinum-based chemotherapy was found. The combination of carboplatin/gemcitabine therefore is considered the preferred first-line treatment choice for patients ineligible for cisplatin but eligible for carboplatin.

7.7.2.3.3 Switch maintenance with immunotherapy after platinum-based chemotherapy

A randomised phase II trial evaluated switch maintenance treatment with pembrolizumab in patients achieving at least stable disease on platinum-based first-line chemotherapy. The primary endpoint of PFS was met (5.4 months vs. 3.0 months, HR: 0.65, p = 0.04) but not the secondary endpoint of OS (22 months vs. 18.7 months, HR: 0.91, 95% CI: 0.52–1.59) [491].

The JAVELIN Bladder 100 study investigated the impact of switch maintenance with the PD-L1 inhibitor avelumab after initial treatment with platinum-gemcitabine chemotherapy. Patients achieving at least stable disease or better after 4–6 cycles of platinum-gemcitabine were randomised to avelumab or best supportive care (BSC). Overall survival was the primary endpoint which improved to 21.4 months with avelumab compared to 14.3 months with BSC (HR: 0.69, 95% CI: 0.56–0.86; p < 0.001). Of patients who discontinued BSC and received subsequent treatment 53% received immunotherapy. Immune-related AEs occurred in 29% of all patients and 7% experienced grade 3 complications [492].

In conclusion, maintenance IO with avelumab is a standard of care for all patients with disease stabilisation on first-line platinum-based chemotherapy.

7.7.2.4 *Treatment of patients unfit for any platinum-based chemotherapy*

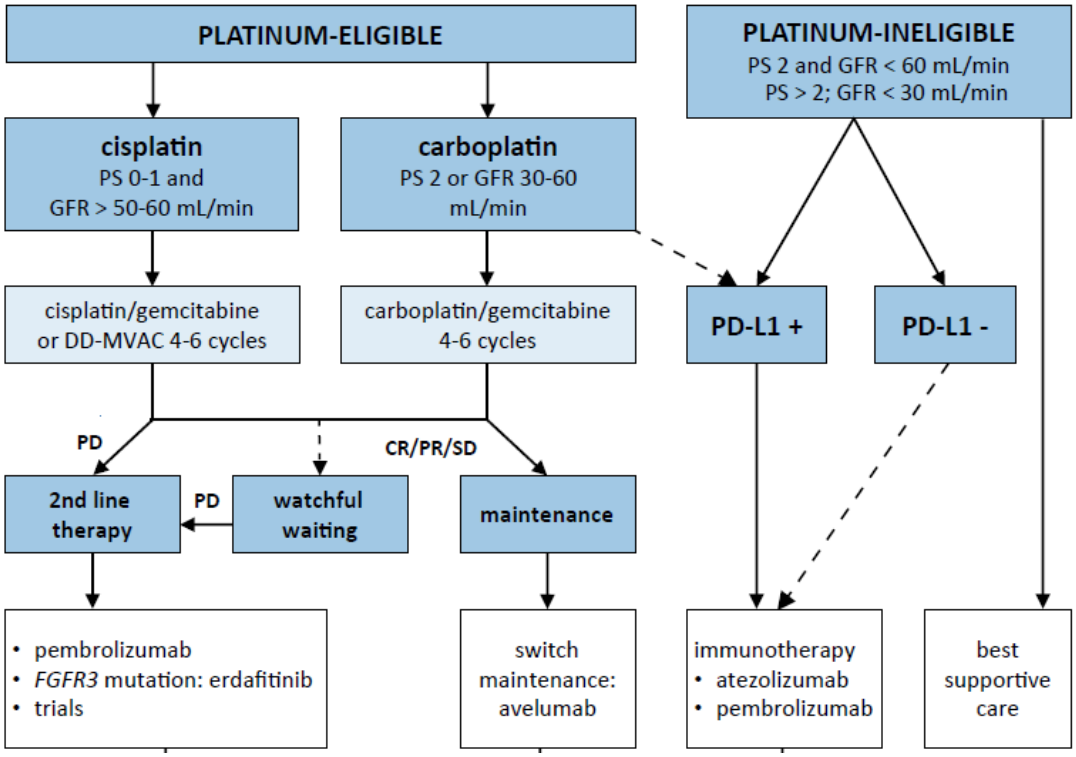
Very limited data exist regarding the optimal treatment for this patient population which is characterised by severely impaired PS (PS > 2) and/or severely impaired renal function (GFR < 30 mL/min). Historically, the outcome in this patient group has been poor. Best supportive care has often been chosen instead of systemic therapy. Most trials evaluating alternative treatment options to cisplatinum-based chemotherapy did not focus specifically on this patient population thereby making interpretation of data difficult. The FDA (but not EMA) has approved pembrolizumab and atezolizumab as first-line treatment for patients not fit to receive any platinum-based chemotherapy regardless of PD-L1 status based on the results of two single-arm phase II trials [489, 490]. These trials have not reported how many patients were unfit for any platinum-based chemotherapy.

7.7.9 ***Summary of evidence and guidelines for metastatic disease***

Summary of evidence	**LE**
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term DFS reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
There is no defined standard therapy for platinum chemotherapy-unfit patients with advanced or metastatic UC.	2b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in highly selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, as they reduce and delay skeletal related events.	1b
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-L1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-L1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-L1 status).	1b
The combination of chemotherapy plus pembrolizumab or atezolizumab and the combination of durvalumab and tremelimumab have not demonstrated OS survival benefit compared to platinum-based chemotherapy alone.	1b
Switch maintenance with the PD-L1 inhibitor avelumab has demonstrated significant OS benefit in patients achieving at least stable disease on first-line platinum-based chemotherapy.	1b

Recommendations	Strength rating
First-line treatment for platinum-fit patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine.	Strong
In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab.	Strong
First-line treatment in patients unfit for platinum-based chemotherapy	
Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-L1 expression (for definitions see text).	Weak

Figure 7.2: Flow chart for the management of metastatic urothelial cancer*



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National Institute for Health and Care Excellence (NICE), 2015 [4,5]

Bladder cancer: diagnosis and management

2019 surveillance of bladder cancer: diagnosis and management (NICE guideline NG2)[5]

Zielsetzung/Fragestellung

This guideline does not include recommendations covering every detail of the diagnosis and treatment of bladder cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of of high quality evidence; or (iv) where NICE guidelines are likely to have most impact.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Keine formalen Konsensusprozesse, jedoch externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist als Hintergrundtext dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert: zuletzt 07.2019

Recherche/Suchzeitraum:

- The Cochrane Library, Medline and Premedline 1946 onwards, Excerpta Medica (Embase) 1974 onwards, Web of Science [specifically Science Citation Index Expanded (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards], Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards, Allied & Complementary Medicine (AMED) 1985 onwards, Psycinfo 1806 onwards. [...] June 2014 should be considered the starting point for searching for new evidence.
- Surveillance report: studies published between 1 April 2014 and 20 November 2018. Immunotherapy is currently limited to use within the cancer drugs fund. […] we will not be covering immunotherapy in this surveillance review.

LoE/GoR

Tabelle 5: 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

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made.

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm
- 'Do not offer' – the intervention will not be of benefit for most patients
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have an 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.

Sonstige methodische Hinweise

- NICE's surveillance team checked whether recommendations in bladder cancer: diagnosis and management (NICE guideline NG2) remain up to date [10]. After considering all evidence and other intelligence and the impact on current recommendations, [...] decided that no update is necessary.

Recommendations: 6 Managing locally advanced or metastatic bladder cancer

6.1.1 First-line chemotherapy

Clinical question: What is the optimal first-line chemotherapy regimen for patients with incurable locally advanced or metastatic bladder cancer?

Evidence Statements

Cisplatin-based chemotherapy

One phase II trial (Hillcoat et al., 1989) of 108 participants provided low quality evidence that there was no difference in overall survival between those treated with single agent Cisplatin (C) therapy or a combination of Cisplatin and Methotrexate (CM). Time to progression was longer with CM, but this difference was only significant during the first 12 months of therapy. Toxicity was greater in the CM arm, including haematological toxicity (26% vs. 7%) and mucositis (19% vs. 0%). Single agent Cisplatin was also compared to MVAC in one trial of 246 participants (Loehrer et al., 1992). Overall survival and progression-free survival were greater for MVAC than Cisplatin alone (low quality evidence). At 6-year follow-up, MVAC still showed a survival advantage over Cisplatin (Saxman et al., 1997). However, combined MVAC was more toxic than Cisplatin, with increased rates of grade 3-4 leukopenia, granulocytopenic fever, and mucositis. There were no differences in treatment-related mortality (4% vs. 0%). There was no evidence about health-related quality of life.

One trial (220 participants) of moderate quality reported increased duration of overall survival (14.2 months vs. 9.3 months) and time-to-progression (9.4 months vs. 6.1 months) with MVAC and granulocyte colony-stimulating factor (GCSF) compared to Docetaxel and Cisplatin with GCSF (Bamias et al., 2004). There were no differences in rates of grade 3-4 thrombocytopenia or anaemia. Neutropenia (36% vs. 19%) and neutropenic sepsis were more common in the MVAC arm. There were no differences in treatment-related mortality. One moderate quality trial (263 participants) compared high-dose intensity MVAC and GCSF (HD-MVAC) with classic MVAC (Sternberg et al., 2001a/2006). After a median of 7.3 years follow-up, HD-MVAC produced a small improvement in risk of death and risk of progression. There were lower rates of whole blood cell toxicity and neutropenic fever with HD-MVAC, with no differences between arms for thrombocytopenia, mucositis and treatment-related mortality. Health-related quality of life was not reported.

One phase III trial (405 participants) of MVAC versus Gemcitabine and Cisplatin (GC) providing high quality evidence reported no differences in overall survival and progression-

free survival between trial arms (von der Maase et al., 2000/2005). Rates of grade 3-4 anaemia and thrombocytopenia were greater in the GC arm, whereas neutropenia and neutropenic sepsis were more common in the MVAC arm. Mean quality of life scores were not reported but the authors state that quality of life (as measured by the EORTC QLQ C30) was maintained on both arms throughout the study with improvements in emotional functioning and pain. One observational study, where oncology professionals were interviewed as patient representatives, provided very low quality evidence that respondents were more likely to choose GC over MVAC for a reduced incidence of neutropenic sepsis, mucositis, or serious weight loss. Respondents were more willing to accept GC over MVAC even when a hypothetical life expectancy was reduced from 60 weeks to 45 weeks.

One randomised phase III trial (130 patients) of dose dense MVAC versus dose dense GC provided low quality evidence of no difference in overall survival or progression-free survival between groups. Grade 3-5 toxicities were reported in 50% of the DD-MVAC group and 44% of the DD-GC group. Two toxicity-related deaths were both in the DD-MVAC arm due to non-neutropenic sepsis (Bamias et al., 2013).

GC was compared with Pacitaxel, Gemcitabine and Cisplatin (PCG) in one randomised phase II trial of 85 patients (Lorusso et al., 2005) and one randomised phase III trial of 626 participants (Bellmunt et al., 2012). The phase III trial provided high quality evidence of no difference in overall survival and progression-free survival between trial arms. However, there was a small effect in the subgroup of patients with primary bladder tumours, with longer overall survival in patients treated with PCG (15.9 vs. 11.9 months, HR 0.80, 95% CI 0.66 to 0.97). Grade 3-4 thrombocytopenia was more common in the GC arm, and grade 3-4 neutropenia was more common in the PCG arm (64% vs. 51%). Health-related quality of life was not reported.

Bamias, A et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. Journal of Clinical Oncology 2004; 22(2): 220-228.

Bamias, A et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Annals of Oncology 2013; 24(4): 1011-1017.

Bellmunt, J et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. Journal of Clinical Oncology 2012; 30(10): 1107-1113.

Hillcoat, BL et al. A randomized trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. Journal of Clinical Oncology 1989; 7(6): 706-709.

Loehrer, PJ et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. Journal of Clinical Oncology 1992; 10(7): 1066-1073.

Lorusso, V et al. Randomised, open-label, phase II trial of paclitaxel, gemcitabine and cisplatin versus gemcitabine and cisplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium. Oncology Reports 2005; 13(2): 283-287.

Saxman, SB et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. Journal of Clinical Oncology 1997; 15(7): 2564-2569.

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von der Maase, H et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. Journal of Clinical Oncology 2000; 18(17): 3068-3077.

von der Maase, H et al. Long-term-survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. Journal of Clinical Oncology 2005; 23(21): 4602-4608.

Cisplatin-based versus carboplatin-based chemotherapy

Bellmunt et al. (1997) provided low quality evidence, comparing MVAC with methotrexate, carboplatin and vinblastine (M-CAVI) in 47 patients. Median disease-related survival was greater in the MVAC arm (hazard ratios were not reported). There were no differences in toxicity between arms. The study was terminated early and failed to reach accrual target. One underpowered trial (84 participants), which was closed early for slow accrual provided very low quality evidence comparing MVAC with carboplatin and paclitaxcel (CaP) (Dreicer et al., 2004). There were no differences between arms for overall survival and progression-free survival. Rates of neutropenia and anaemia were higher in the MVAC arm, but there were no differences in rates of thrombocytopenia and treatment-related mortality. It was reported that there were no differences in quality of life over time by treatment arm, but low numbers of participants were assessed for quality of life, which limits the precision of this outcome. One underpowered trial (110 participants) provided very low quality evidence of no difference in overall survival, time-to-progression, and toxicity between patients treated with Gemcitabine and Cisplatin versus Gemcitabine and Carboplatin (Dogliotti et al., 2007).

Four trials comparing cisplatin-based chemotherapy with carboplatin-based chemotherapy were included in the meta-analysis by Galsky et al. (2012). Very low quality evidence from two studies showed no difference in survival rate at 12 months (RR 0.76, 95% CI 0.56 to 1.07). Progression-free survival was not reported consistently across studies and could not be pooled in a meta-analysis. Therefore, overall tumour response rates and complete tumour response rates were pooled and risk ratios (95% CIs) were calculated. A partial tumour response was defined as a 50% reduction in bidimensional tumour measurements and a complete response as a resolution of radiographic abnormalities. A majority of patients had a performance status of 0 to 1 with adequate renal function. The meta-analysis demonstrated a higher likelihood of achieving an overall response (RR 1.34, 95% CI 1.04 to 1.71) and a complete response (RR 3.54, 95% CI 1.48 to 8.49) with cisplatin-based chemotherapy. However, this analysis is based on three small phase II studies and one phase III trial which was closed early due to poor accrual. The chemotherapy agents used and the doses of carboplatin used differed across studies.

Chemotherapy in 'unfit' patients

Moderate quality evidence for overall survival and progression-free survival was provided by one phase III RCT (238 participants) comparing Gemcitabine & Carboplatin (GCarbo) with Methotrexate & Carboplatin & Vinblastine (M-CAVI) (De Santis et al., 2012) in patients unfit for cisplatin-based therapy. After a median of 4.5 years follow-up there were no differences in overall survival (HR 0.94, 95% CI 0.72 to 1.02) and progression-free survival (HR 1.04, 0.8 to 1.35) between the two treatments. GCarbo produced a lower rate of severe acute toxicity than M-CAVI (9% vs. 21%). There were no differences between treatments for changes in health-related quality of life from baseline to end of cycle 2, although mean scores were not reported and there was less than 50% response rate after the baseline assessment.

Bellmunt, J et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer 1997; 80(10): 1966-1972.

De Santis, M et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of Clinical Oncology 2012; 30(2): 191-199.

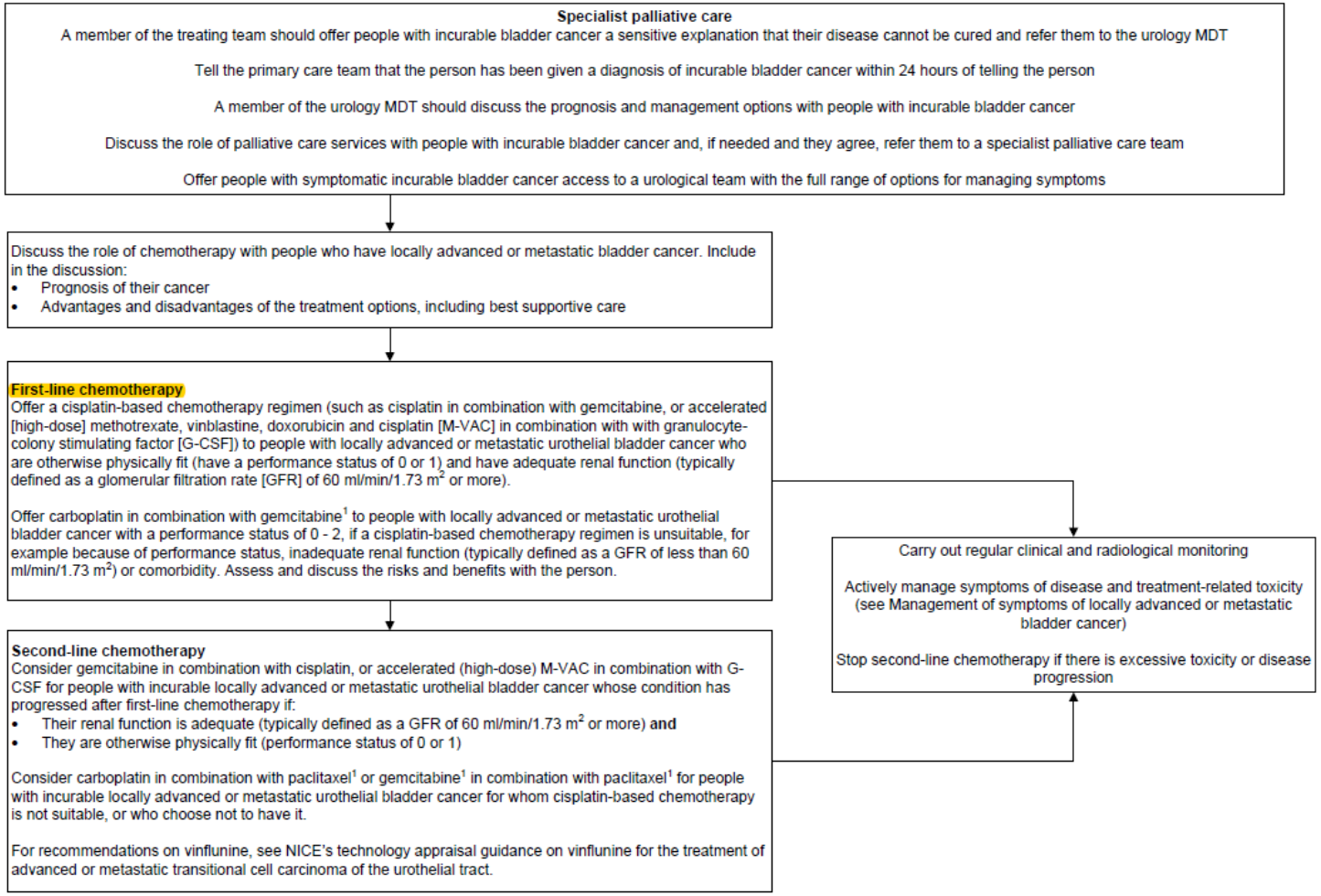
Dogliotti, L et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. European Urology 2007; 52(1): 134-141.
Dreicer, R et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer 2004; 100(8): 1639-1645.
Galsky, MD et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Annals of Oncology 2012; 23(2): 406-410.

Recommendations	**Discuss the role of first-line chemotherapy with people who have locally advanced or metastatic bladder cancer. Include in your discussion:** • **prognosis of their cancer and** • **advantages and disadvantages of the treatment options, including best supportive care.** **Offer a cisplatin-based chemotherapy regimen (such as cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [M-VAC] in combination with granulocyte-colony stimulating factor [G-CSF]) to people with locally advanced or metastatic urothelial bladder cancer who are otherwise physically fit (have an Eastern Cooperative Oncology Group [ECOG] performance status of 0 or 1) and have adequate renal function (typically defined as a glomerular filtration rate [GFR] of 60 ml/min/1.73 m^2 or more).** **Offer carboplatin in combination with gemcitabine[h] to people with locally advanced or metastatic urothelial bladder cancer with an ECOG performance status of 0 - 2, if a cisplatin-based chemotherapy regimen is unsuitable, for example, because of ECOG performance status, inadequate renal function (typically defined as a GFR of less than 60 ml/min/1.73 m^2) or comorbidity. Assess and discuss the risks and benefits with the person.** **For people having first-line chemotherapy for locally advanced or metastatic bladder cancer:** • **carry out regular clinical and radiological monitoring and** • **actively manage symptoms of disease and treatment-related toxicity and** • **stop first-line chemotherapy if there is excessive toxicity or disease progression.**
Relative value placed on the outcomes considered	All the outcomes specified in the PICO were reported in the evidence. The GDG considered progression-free survival, overall survival, and toxicity as the most important outcomes. Improvements in these outcomes were considered the most meaningful endpoints for patients/patient care. Survival is threatened by metastatic or locally advanced disease and overall prognosis is poor. Therefore, significant improvement in survival associated with chemotherapy treatment is considered to be an important outcome. Chemotherapy treatments have toxic adverse events so the GDG considered regimens delivering lower levels of toxicity. Tumour response was not specified in the PICO but was reported in the systematic review of cisplatin versus non-cisplatin based chemotherapy (Galsky, 2012) as no other outcomes could be pooled. Tumour response was considered by the GDG as a surrogate outcome for treatment effectiveness.
Quality of the evidence	The evidence ranged from low to high quality across comparisons as

	assessed with GRADE. The GDG considered the limitation of the post-hoc analysis of overall survival for the subgroup of bladder tumours in the PCG trial (Bellmunt, 2012). Post-hoc selections can introduce bias. Less weight was placed on the positive outcome reported in the PCG trial due to these limitations. In light of this concern, PCG was recommended as an option to consider because the GDG did not believe the evidence warranted recommending offering this treatment as the best option. The recommendation that patients should be carefully monitored for toxicity was based on clinical experience. No specific evidence on how to monitor patients was examined, although all included trials stopped treatment if patients progressed or if there was excessive toxicity. The GDG reached consensus that treatment options, including the use of chemotherapy and best supportive care should be discussed with the patient. The GDG considered making a research recommendation for a trial of GC versus HDMVAC but considered this unlikely to be funded or to have sufficient support to take forward. Low quality health economic evidence was identified. The economist highlighted a potential bias in that it was a manufacturer sponsored study. Other limitations of the study include the cost of drug was not included in sensitivity analysis, utility data was not reported directly from patients, drug costs have changed since analysis conducted (come off patent),the comparator of MVAC is outdated (HDMVAC is now more widely used). The GDG therefore considered the economic analysis to be of limited value to current practice.
Trade-off between clinical benefits and harms	The main benefits of the recommendations made are that they provide clear guidance for patients to be offered chemotherapy and for which patient groups cisplatin-based chemotherapy is appropriate. This should improve outcomes for patients in terms of overall and progression-free survival. The recommendations made may increase the use of cisplatin-based chemotherapy and therefore increased toxicity and adverse effects may be expected. The GDG considered survival to be more important than toxicity and that patients are likely to consider the survival advantage and toxicity when deciding on treatment. The GDG considered that the potential for increased toxicity is mitigated by recommending the careful monitoring of patients for adverse events and discontinuing treatment if there is excessive toxicity. There was weak evidence to suggest a benefit of doublet chemotherapy as second line chemotherapy, when indirectly compared with best supportive care or single agent chemotherapy. The GDG therefore recommended doublet chemotherapy be considered. The GDG considered making a 'do not offer' recommendation for single agent chemotherapy, but decided after extensive discussion and following stakeholder feedback that there was insufficient evidence to make a

	recommendation either way.
Trade-off between net health benefits and resource use	The GDG considered that the economic evidence identified was not applicable to current practice and no economic model was built. The potential costs of the recommendations made include the increased use of chemotherapy and GCSF. The potential savings include the avoidance of ineffective chemotherapy and possibly the avoidance or delay of the costs of palliative care. Improved survival means that chemotherapy is potentially cost-effective in cost/QALY terms.
Other considerations	The GDG considered that the recommendations equalise access to treatment for patients who currently don't have access. Patients who are both suitable and unsuitable for cisplatin-based chemotherapy are accounted for in recommendations. The GDG considered that the implementation of these recommendations would not cause a significant change in current practice.

Management of locally advanced or metastatic bladder cancer



[1] Although this use is common in UK clinical practice, at the time of publication (February 2015), this intervention did not have UK marketing authorisation for this indication. . The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2023) am 30.01.2023

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
2	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
3	(urotheli* OR transitional OR bladder):ti,ab,kw
4	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma*):ti,ab,kw
5	#3 AND #4
6	#1 OR #2 OR #5
7	#6 with Cochrane Library publication date from Jan 2018 to present

Systematic Reviews in PubMed am 30.01.2023

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

#	Suchfrage
1	"carcinoma, transitional cell"[MeSH Major Topic] AND "carcinoma, transitional cell/therapy"[mh]
2	"urinary bladder neoplasms"[MeSH Major Topic] AND "urinary bladder neoplasms/therapy"[mh]
3	((urotheli*[tiab]) OR transitional[tiab]) OR bladder[tiab]
4	((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR cancer*[tiab]
5	((((((Neoplasm Metastasis[mh]) OR Neoplasm Recurrence, Local[mh]) OR advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab])
6	#3 AND #4 AND #5
7	(#6) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
8	#1 OR #2 OR #7
9	(#8) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health

#	Suchfrage
	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]))))))
10	(#9) AND ("2018/01/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 30.01.2023

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

#	Suchfrage
1	"carcinoma, transitional cell"[MeSH Major Topic]
2	"urinary bladder neoplasms"[MeSH Major Topic]
3	((urotheli*[ti]) OR transitional[ti]) OR bladder[ti]
4	((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR cancer*[tiab]
5	#3 AND #4
6	#1 OR #2 OR #5

#	Suchfrage
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
8	(#7) AND ("2018/01/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 30.01.2023

- 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)

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

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

Verfahrens-Nr.: 2023-B-166

Verfasser	
Institution	S3-Leitliniengruppe Harnblasenkarzinom DGU Deutsche Gesellschaft für Urologie DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
Sachverständige	
Datum der Erstellung	25. Juli 2023

Indikation
Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinom
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Standard in der Behandlung von Patientinnen und Patienten (Pat.) mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinoms - Platin-basierte Chemotherapie - gefolgt von einer Erhaltungstherapie mit Avelumab bei Pat., die unter der Chemotherapie eine mindestens stabile Erkrankung erreichen Standard in der Behandlung von Pat. mit lokal fortgeschrittenem oder metastasiertem Urothelkarzinoms, die nicht für eine Platin-basierte Therapie geeignet sind, ist eine - Immuncheckpoint-Inhibitor-basierte Therapie bei Nachweis der Expression von PD-L1 - Monochemotherapie bei fehlender Expression von PD-L1 - Best Supportive Care. <u>Fragestellung</u> Dies ist eine weitere Stellungnahme zum lokal fortgeschrittenen oder metastasierten Urothelkarzinom im Rahmen der Einbindung der Fachgesellschaften in die Beratungen des G-BA.

Stand des Wissens

Behandlungsstandard in der Erstlinientherapie von Pat. mit einem lokal fortgeschrittenen oder metastasierten Urothelkarzinom ist die systemische, Platin-basierte Kombinationstherapie. Sofern Pat. Cisplatin-geeignet sind, soll eine Cisplatin-basierte Kombinationschemotherapie (Gem/Cis, M-VAC oder HD MVAC) verabreicht werden [1-4]. Zeigt sich unter dieser Behandlung eine zumindest stabile Tumorerkrankung, schließt sich daran eine Erstlinienerhaltungstherapie mit dem Immuncheckpoint-Inhibitor Avelumab an.

Cisplatin-basierte Kombinationstherapien sind seit Jahren Grundpfeiler der Systemtherapie metastasierter, urothelialer Karzinome. Drei Kombinationstherapien haben sich dabei in der Erstlinie durchgesetzt: Methotrexat, Vinblastin, Adriamycin und Cisplatin (MVAC), Gemcitabin und Cisplatin (GC) sowie ein intensiviertes MVAC-Schema mit begleitender Gabe von Granulozyten-stimulierendem Wachstumsfaktor (HD-MVAC). Das Gesamtüberleben der Pat. konnte durch den Einsatz dieser Regime von etwa 3 – 6 Monaten auf etwa 12 – 16 Monate verlängert werden [5, 6]. Im direkten Vergleich von MVAC mit GC konnte für keines der Therapieregime ein signifikanter Überlebensvorteil gegenüber der jeweils anderen Therapie gezeigt werden [5]. Eine Behandlung mit GC war im Hinblick auf das Auftreten von Komplikationen, insbesondere eines neutropenen Fiebers, weniger toxisch als eine Behandlung mit MVAC. Das intensivierte HD-MVAC-Schema war ebenfalls weniger toxisch als das „klassische“ MVAC-Schema, ein direkter Vergleich zwischen HD-MVAC und GC wurde allerdings bislang nicht durchgeführt [3, 4]. Durchgesetzt in der deutschen Versorgungspraxis hat sich aufgrund des günstigeren Nebenwirkungsprofils die Kombination aus Gemcitabin und Cisplatin [1, 2].

Die Eignung für eine Cisplatin-Therapie orientiert sich an den MSKCC-Kriterien (Cisplatin geeignete Pat.: ECOG 0-1, Kreatinin-Clearance >60 ml/min, kein Hörverlust ≥ Grad 2, keine Neuropathie ≥ Grad 2, NYHA ≤2) [7]. Ausgewählte Pat. mit gutem ECOG-Performance Status (0-1), mäßig eingeschränkter Nierenfunktion (GFR 40-60 ml/min) und ohne weitere Komorbiditäten können Cisplatin in aufgeteilten Dosen erhalten.

Bei Cisplatin-ungeeigneten Pat. wird weitergehend zwischen Platin-geeigneten und -ungeeigneten Pat. differenziert. Bei Pat., die entsprechend den MSKCC-Kriterien (Cisplatin geeignete Pat.: ECOG 0-1, Kreatinin-Clearance >60 ml/min, kein Hörverlust ≥ Grad 2, keine Neuropathie ≥ Grad 2, NYHA ≤2, siehe auch oben) nicht für eine Cisplatin-basierte Therapie in Frage kommen, besteht die Möglichkeit Cisplatin durch Carboplatin zu ersetzen. Dies betrifft etwa die Hälfte der Pat. mit einem metastasierten und/oder nicht resezierbaren Urothelkarzinom [3, 4]. Aufgrund der relativ schlechteren Wirksamkeit Carboplatin-basierter gegenüber Cisplatin-basierter Kombinationstherapie (s.u.) können entsprechend den aktuellen Empfehlungen der aktuellen S3-Leitlinien ausgewählte Pat. mit gutem ECOG-Performance Status (0-1), mäßig eingeschränkter Nierenfunktion (GFR 40-60 ml/min) und ohne weitere Komorbiditäten mit Cisplatin in aufgeteilten Dosen behandelt werden [1, 2].

Die Wirksamkeit unterschiedlicher Carboplatin-basierter Kombinationstherapien in der Erstlinienbehandlung von erwachsenen Pat. mit nicht resezierbarem oder metastasiertem Urothelkarzinom, die nicht für eine Cisplatin-basierte Therapie eignen, wurde in drei randomisierten Studien (1x Phase II/III, 2x Phase II) untersucht. In der EORTC-Phase II/III Studie 30986 (n=237 Pat.) wurde eine Behandlung dieser Pat. mit Carboplatin in Kombination mit Gemcitabin (GemCarbo) oder Methotrexat, Carboplatin, Vinblastin (M-CAVI) verglichen. Die Ansprechraten beider Regime lagen

mit 30 – 40 % ebenso wie das Gesamtüberleben mit etwa 8 – 9 Monaten niedriger als bei Cisplatin-basierten Kombinationen. Bei gleichem Ansprechen zeigte sich für GemCarbo allerdings eine deutlich niedrigere Rate an Nebenwirkungen [8]. In einer weiteren Phase II Studie (n=96) wurde eine Behandlung mit Vinflunin in Kombination mit Gemcitabin (VinGem) oder Carboplatin (VinCarbo) verglichen. Während die Ansprechrate für den VinGem Arm (44%) deutlich höher als für den VinCarbo Arm (29%) ausfiel, war das Gesamtüberleben der Pat. in beiden Therapiearmen vergleichbar (VinGem 14,0 Monate, VinCarbo 12,8 Monate) [9]. Die dritte randomisierte Studie (GETUG V01, Phase II, n=44) wurde vorzeitig abgebrochen, da sich im Kombinationstherapiearm (Gemcitabin und Oxaliplatin) in einer Zwischenauswertung ein schlechteres Therapieansprechen (27%) im Vergleich zum Monotherapiearm mit Gemcitabin (43%) zeigte [10].

Wenn durch die Platin-basierte Chemotherapie ein Tumoransprechen oder ein stabiler Erkrankungsverlauf erreicht wird, ist eine anschließende Immunerhaltungstherapie der Behandlungsstandard. Der Vorteil einer Immunerhaltungstherapie mit dem PD-L1-Inhibitor Avelumab gegenüber einer alleinigen Tumornachsorge nach einer Erstbehandlung mit einer platin-basierten Chemotherapie konnte in der JAVELIN100 Studie gezeigt werden. Pat., die nach vier bis sechs Chemotherapiezyklen eine zumindest stabile Erkrankung erreicht hatten, wurden nach Randomisierung entweder mit Avelumab oder einer ausschließlichen Nachsorge (BSC) behandelt. Hinsichtlich des primären Endpunktes (Gesamtüberleben) zeigte sich ein signifikanter Vorteil von Avelumab (21,4 Monate) gegenüber einer BSC (14,3 Monaten) (HR: 0,69, 95% CI: 0,56-0,86; $p < 0,001$) [11].

Bei Platin-ungeeigneten Pat. ist eine Behandlung mit einem Immuncheckpoint-Inhibitor (Atezolizumab oder Pembrolizumab) möglich, falls der Patient einen positiven PD-L1-Status aufweist. Der Einsatz von Immuncheckpoint-Inhibitoren wurde bei Pat. mit nicht resezierbarem oder metastasiertem Urothelkarzinom, die nicht für eine Cisplatin-basierte Therapie geeignet sind, in zwei nicht-randomisierten Phase II Studien untersucht. In einer dieser Studien (IMvigor 210, n=119 Pat.) wurden Cisplatin-ungeeignete Pat. mit dem PD-L1-Inhibitor Atezolizumab behandelt. Hier zeigte sich ein medianes Gesamtüberleben der eingeschlossenen Pat. von 15,4 Monaten bei einem objektiven Ansprechen von 24% [12]. In einer weiteren Phase II-Studie (KEYNOTE-052, n=374), in der der Einsatz des PD1-Inhibitors Pembrolizumab untersucht wurde, waren die Ergebnisse vergleichbar (medianes Gesamtüberleben: 11,5 Monate, objektives Ansprechen: 24%) [13]. Weiterhin fanden sich in beiden Studien Hinweise darauf, dass Pat. mit einem Tumoransprechen im Gegensatz zu einer Chemotherapie langfristig von einer Behandlung zu profitieren scheinen.

Ist eine Platin-basierte Kombinationstherapie aufgrund der Begleiterkrankungen oder des Allgemeinzustandes des Pat. nicht möglich und ist keine PD-L1 Expression nachweisbar, kann ggf. auf eine Monochemotherapie ausgewichen geben. Die Datenlage zum Einsatz von Monotherapien in der Erstlinienbehandlung von Pat., die nicht für eine Cisplatin-basierte Behandlung geeignet sind, ist auf kleine nicht-randomisierte Phase II Studien beschränkt [1, 2]. Zum Einsatz kommt z.B. eine Monotherapie mit Gemcitabin [8].

Neben den bereits zuvor angeführten Behandlungsoptionen stellt der Verzicht auf tumorspezifische Therapien zugunsten einer rein palliativ-symptomatischen Behandlung im Sinne von Best Supportive Care eine weitere Option dar. Dies betrifft insbesondere Pat. in reduziertem Allgemeinzustand oder mit hoher Tumorlast (z. B. ausgedehnte hepatische Metastasierung).

Alle Pat. mit fortgeschrittenem oder metastasiertem Urothelkarzinom sollten die Möglichkeit haben, an klinischen Studien teilzunehmen. Die jeweiligen Therapieoptionen werden im interdisziplinären Tumorboard besprochen [1, 2].
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Ja, diese sind oben beschrieben. Zusätzlich zum Kriterium „geeignet für Platin-basierte Therapie“ ist vor allem die PD-L1-Expression relevant.

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