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ORIGINAL RESEARCH

Comparison of single agent versus combined chemotherapy in previously treated patients with advanced urothelial carcinoma: a meta-analysis

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Background: Platinum-based chemotherapy is the standard treatment for advanced urothelial cancer (UC) and is generally used in the first-line setting. However, the optimal salvage treatment for previously treated UC patients is unclear. We conducted a systematic review of published clinical trials of single agent versus combined chemotherapy as salvage treatment in previously treated UC patients.

Methods: Trials published between 1994 and 2015 were identified by an electronic search of public databases (MEDLINE, EMBASE, Cochrane library). All relevant studies were independently identified by two authors for inclusion. Demographic data, treatment regimens, objective response rate (ORR), disease control rate (DCR), median progression-free and overall survival (PFS, OS), and grade 3/4 toxicities were extracted and analyzed using Comprehensive Meta Analysis software (Version 2.0).

Results: Fifty cohorts with 1,685 patients were included for analysis: 814 patients were treated with single agent chemotherapy and 871 with combined chemotherapy. Pooled OS was significantly higher at 1 year for combined chemotherapy than for single agent (relative risk [RR] 1.52; 95% CI: 1.01–2.37; P=0.03) but not for 2-year OS (RR 1.31; 95% CI: 0.92–1.85; P=0.064). Additionally, combined chemotherapy significantly improved ORR (RR 2.25; 95% CI: 1.60–3.18; P<0.001) and DCR (RR 1.12; 95% CI: 1.01–1.25, P=0.033) compared to single agent for advanced UC patients. As for grade 3 and 4 toxicities, more frequencies of leukopenia and thrombocytopenia were observed in the combined chemotherapy than in single agent group, while equivalent frequencies of anemia, nausea, vomiting, and diarrhea were found between the two groups.

Conclusion: In comparison with single agent alone, combined chemotherapy as salvage treatment for advanced UC patients significantly improved ORR, DCR, and 1-year OS, but not 2-year OS. Our findings support the need to compare combined chemotherapy with single agent alone in the salvage setting in large prospective trials due to its potential survival benefit in advanced UC patients.

Keywords: advanced urothelial cancer, salvage chemotherapy, cytotoxic agents, meta-analysis, efficacy

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Introduction

Urothelial cancer (UC), also called transitional cell carcinoma, accounts for more than 90% of bladder cancers, with more than 350,000 newly diagnosed cases, and causes approximately 150,000 deaths per year worldwide.[1] Approximately 75%–80% of cases of urothelial tumors present with non-muscle invasive disease; however, the remaining cases of advanced (muscle invasive) disease can progress to metastatic disease, and the prognosis of these patients is very poor.[2] Currently, platinum-based chemotherapy

is the standard of care for advanced UC patients. These chemotherapy regimens include combinations such as cisplatin and gemcitabine and methotrexate, vinblastine, doxorubicin, and cisplatin.[3] However, platinum resistance occurs rapidly and nearly 80% of cases relapse. For these patients, there remains no consensus regarding optimal treatment. In the first and largest randomized Phase-III trial conducted by Bellmunt et al in 2009,[4] vinflunine chemotherapy demonstrated a 8.6% response rate with a 2.3-month survival benefit; this led to the approval of vinflunine as second-line therapy for UC by the European Medicines Agency (EMA) in 2009 but not in the USA. Recently, many cytotoxic agents,[5–11] as single agent or in combination, have been extensively investigated as candidate second-line chemotherapies for advanced UC. However, to our best knowledge, there are no head-to-head comparison data available for single agent versus combined chemotherapy in the treatment of previously treated patients with UC. Therefore, we performed a systematic review and meta-analysis of published data to compare treatment outcomes with single agent versus combined chemotherapy for the management of previously treated patients with UC.

Methods
Study design
We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[12]

Identification and selection of studies
To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of four databases, including EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to July 2015. The search included the following terms: "urothelial neoplasms", "urothelial carcinoma", "urothelial cancer", "chemotherapy", "previously treated", "refractory", "salvage therapy", and "clinical trials". Additional references were searched through manual searches of the reference lists and specialist journals. No language restrictions were applied.

Study populations (referred to hereafter as cohorts) with the following criteria were eligible for the study: 1) patients with UC who were refractory to previous chemotherapy; 2) patients who were under treatment with combined chemotherapy or single agent chemotherapy (patients who received molecular agent alone or chemotherapy plus molecular

targeted agents were excluded for analysis in our study); 3) patients with reported outcomes of interest (ie, objective response rate [ORR], disease control rate [DCR], and 1- and 2-year overall survival [OS]; and 4) patients from an original study (ie, randomized controlled trial, non-randomized clinical trial, observational studies, or case series).

Data extraction
Two investigators screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap.

The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: author, study design, study period, median age, interventions (chemotherapy regimens and dose), sample size, and outcomes of interest. We defined outcomes of interest as ORR, DCR, and 1- and 2-year OS. To assess quality, since we included non-comparative (uncontrolled) studies in our systematic review and meta-analysis, we used the Newcastle-Ottawa quality assessment scale.[13] We selected items that focused on representativeness of study patients, demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, and adequacy of follow-up.

Statistical analysis
We prespecified the analysis plan in the protocol. We analyzed all patients who started single agent or combined chemotherapy, regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for both single agent and combined chemotherapy. We pooled log-transformed event rates with DerSimonian and Laird random-effect models and assessed heterogeneity using chi-square-based Q statistic test.[14] We used the test of interaction proposed by Altman and Bland[15] to compare log-transformed rates of outcomes between single agent and combined chemotherapy. A statistical test with a P-value less than 0.05 was considered significant. To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with I^2 greater than 50% indicating high heterogeneity. We did all statistical

analyses with comprehensive meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA).

Results

Search results

A total of 569 studies were identified from the database search, of which 70 reports were retrieved for full-text evaluation. Fifty cohorts from 49 trials met the inclusion criteria and were included in this systematic review[4–11,16–56] (Figure 1). We did not find randomized controlled trials or controlled studies that compared single agent with combined chemotherapy in previously treated patients with UC directly. Table 1 shows the characteristics of the included studies. Overall, 1,685 patients previously treated with advanced UC were included, with a median age of 64 years for the single agent group and 65 years for the combined chemotherapy group. The median progression-free survival (PFS) and OS were higher in combined chemotherapy cohorts than single agent cohorts, while the median age did not significantly differ between groups (Table 2).

Methodological quality of the included studies was fair; most studies provided adequate outcome ascertainment, enrolled a representative sample of patients, and had an acceptable length of follow-up (Figure 2). However, comparative evidence was at high risk of bias because we compared data across studies not within them, and selection bias was likely to be present. Assessment of publication bias was not done because data would be unreliable in view of the few studies included for each treatment group and high heterogeneity ($I^2 > 50\%$) in most analyses.
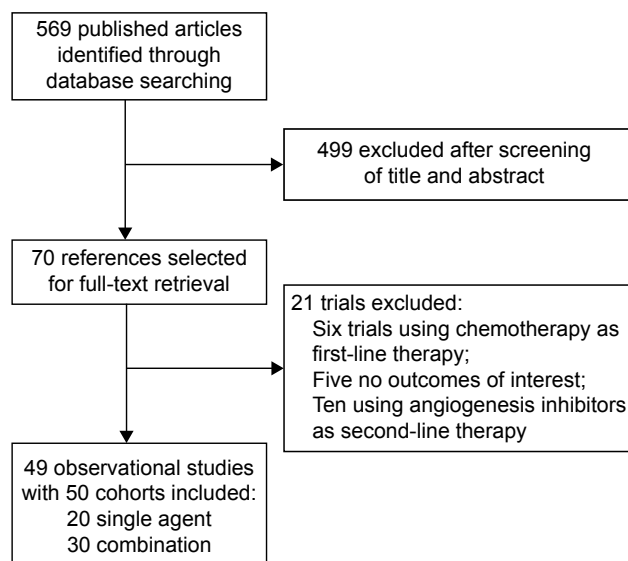
Figure I Selection process for clinical trials included in the meta-analysis.

Pooled incidence of primary outcomes

A total of 1,556 patients were included for ORR analysis. The pooled event rate of ORR for combination chemotherapy was higher than that of single agent alone (34.5% vs 15.3%, Table 3). A higher incidence of DCR and 1-year OS was observed in combination chemotherapy (56.6% and 38.5%, respectively), while comparable incidence of 2-year OS was found between combination chemotherapy and single agent alone (16.1% vs 12.3%, Table 3).

Efficacy comparison between combination chemotherapy and single agent

The pooled event rate of OS for combined chemotherapy was significantly higher than that for single agent chemotherapy at 1 year (relative risk [RR] 1.52; 95% confidence interval [CI]: 1.01–2.37; P=0.03) but not for 2-year OS (RR 1.31; 95% CI: 0.92–1.85; P=0.064, Table 3). Additionally, ORR and DCR were significantly different between combined chemotherapy and single agent ($P < 0.001$ and P=0.033, respectively) (Table 3).

Toxicity

Table 4 shows the overall occurrence of high-grade ($\geq$ grade 3) toxic effects with single agent versus combined chemotherapy. There were significantly more toxicities of leukopenia and thrombocytopenia in the combined chemotherapy than in single agent group ($P < 0.001$ and P=0.024, respectively). While more incidence of fatigue was observed in single agent group when compared to combined chemotherapy (RR 0.17, 95% CI: 0.07–0.42, $P < 0.001$). Additionally, equivalent frequencies of anemia, nausea, vomiting, and diarrhea were found between single agent and combined chemotherapy (Table 4).

Discussion

UC is the most common cancer of the urinary tract. Although platinum-based chemotherapy regimen is regarded as the gold standard for treating advanced UC patients,[57] there is no established treatment for these patients with progressive disease other than the first-line platinum-based chemotherapy. Due to the aggressive and rapid fatal disease course of advanced UC, the development of systematic chemotherapy using combinations of agents is rational for the salvage treatment of this disease, especially in those patients with good performance status. However, to the best of our knowledge, there is lack of head-to-head comparison data available for combination chemotherapy versus single agent alone as salvage treatment for advanced UC patients. As a result, we conducted this

Table 1 Baseline characteristics of 50 cohort groups for meta-analysis

Author	Study design	Patients, n	Chemotherapy regimen	Median age, years	Median PFS, months	Median OS, months
Matsumoto et al[16]	R	10	GEM + Nadaplatin	67	8.8	5
Maolake et al[17]	R	27	Tegafur-uracil	74	11.9	NR
Naiki et al[18]	R	38	GEM + Doc	66	10.8	4.4
Morales-Barrera et al[19]	R	22	Doc	71	3.12	1.67
Lee et al[20]	R	28	M-VAC	64	11.4	4.9
Rozzi et al[21]	P	23	Pegylated liposomal doxorubicin	62	6.3	4.1
Ko et al[22]	P	48	Nanoparticle albumin-bound paclitaxel	66	10.8	6
Halim and Abotouk[23]	P	40	MTX + PTX + EPI + CBP	62	12.5	12
Bhattacharyya et al[24]	P	18	MFI	63.5	5.4	3.4
Tsuruta et al[25]	P	16	GEM + CBP + Doc	68	12.6	5
Rozzi et al[26]	P	35	EPI + PTX	64	12.6	7.6
Kitamura et al[27]	P	45	PTX + IFO + Nedaplatin	68	8.9	4
Joung et al[28]	R	21	PTX + DDP	64	9	3
Ikeda et al[29]	R	24	GEM + PTX	64.5	12.4	6.1
Albers et al[30]	P	81	GEM + PTX short-term	63.9	7.8	4
			GEM + PTX long-term	65.1	8	3.1
Tanji et al[31]	R	32	GEM + DDP	74	13	5
Suyama et al[32]	R	33	GEM + PTX	66.1	11.3	NR
Srinivas and Harshman[33]	P	11	DOC + L-OHP	65	7	NR
Joly et al[34]	P	45	PTX	64	6.9	3.2
Dumez et al[35]	P	21	Plitidepsin	64	2.3	1.4
Bellmunt et al[50]	P	253	Vinflunine	NR	6.9	NR
Lassiter et al[36]	P	23	Piritrexim	66.2	NR	NR
Kanai et al[37]	P	20	GEM + PTX	62.9	11.5	NR
Han et al[38]	P	30	M-VAC	64	10.9	5.3
Uhm et al[39]	P	28	PTX + DDP	61	10.3	6.2
Matsumoto et al[40]	R	10	GEM + PTX	66	10.3	4.1
Lin et al[41]	P	23	GEM + IFO	66	4.8	3.5
Kouno et al[42]	P	35	PTX + CBP	67	7.9	3.7
Galsky et al[43]	P	13	Pemetrexed	69	NR	NR
Sweeney et al[9]	P	47	Pemetrexed	64	9.6	2.9
Fechner et al[44]	P	30	GEM + PTX	66	13	8.5
Culine et al[45]	P	51	Vinflunine	63	6.6	3
Winquist et al[10]	P	20	L-OHP	64	7	1.5
Vaishampayan et al[46]	P	44	PTX + CBP	64.6	6	4
Hoshi et al[47]	P	16	GEM + CBP	68	NR	NR
Vaughn et al[48]	P	31	PTX	66	7.2	2.2
Pagliaro et al[49]	P	51	GEM + IFO	65	9.5	NR
Bellmunt et al[50]	P	20	MTX + PTX	NR	5	3
Albers et al[5]	P	30	GEM	NR	8.7	4.9
Stenberg et al[51]	P	41	GEM + PTX	NR	14.4	NR
Krege et al[6]	P	22	DOC + IFO	61	NR	NR
De Mulder et al[52]	P	43	5-FU + DDP	61	4.9	2.33
Sweeney et al[53]	P	26	PTX + IFO	66	NR	NR
Lorusso et al[7]	P	31	GEM	64	5	3.8
Witte et al[54]	P	56	IFO	NR	NR	NR
Pronzato et al[55]	P	20	IFO	NR	NR	NR
Papamichael et al[8]	P	14	PTX	68	NR	NR
McCaffrey et al[11]	P	30	Doc	NR	9	NR
Dreicer et al[56]	P	9	PTX	63	NR	NR

Abbreviations: PFS, progression-free survival; OS, overall survival; R, retrospective; P, prospective; GEM, gemcitabine; Doc, docetaxel; PTX, paclitaxel; IFO, ifosfamide; CBP, carboplatin; 5-FU, 5-fluorouracil; DDP, cisplatin; MTX, methotrexate; L-OHP, oxaliplatin; EPI, epirubicin; M-VAC, methotrexate plus vinblastine plus dororubicin plus cisplatin; MFI, methotrexate plus fluorouracil plus irinotecan; NR, not reported.

Table 2 Baseline characteristics of single agent versus combined chemotherapy

Characteristics	Single agent	Combined chemotherapy	*P*-value
Cohorts (n)	20	30	–
Patients (n)	814	871	–
Median age (years)	64	65	0.58
Median PFS, m	3.0	4.25	0.022
Median OS, m	6.95	10.3	0.012

**Abbreviations:** PFS, progression-free survival; OS, overall survival; m, months.

systematic review and meta-analysis to evaluate the efficacy of combination chemotherapy versus single agent alone as salvage treatment for advanced UC patients.

A total of 1,685 advanced UC patients from 50 cohorts are included for analysis. Based on our pooled results, we found that combined chemotherapy resulted in a statistically increased ORR, DCR, and 1-year OS but not for 2-year OS. In addition, our study indicated that combination chemotherapy was associated with more frequencies of grade 3 and 4 myelosuppression toxicities, while equivalent frequencies of anemia, nausea, vomiting, and diarrhea were found between single agent and combined chemotherapy except for fatigue. However, clinicians should be cautious when interrupting these results due to the limitation of our studies, and more evidence is still required to identify patients who will most likely benefit by the appropriate combination chemotherapy.

After we completed our study, a similar analysis of taxanes-containing combination chemotherapy versus single agent taxane in previously treated UC patients was published.[58] This latter study revealed that taxanes-containing chemotherapy significantly is associated with an improved OS (hazard ratio 0.60; 95% CI: 0.45–0.82; *P*<0.001) and PFS (hazard ratio 0.61; 95% CI: 0.49–0.77; *P*<0.001). Our study is different on several counts. First, our study included both taxanes and other chemotherapy drugs as salvage treatment for advanced UC patients, resulting in a larger sample size (1,685 versus 370 patients). Secondly, our study also assessed the ORR, DCR, and grade 3/4 toxicities with combination chemotherapy versus single agent. Importantly, despite literature review from two separate groups, using different methodology, and including some nonoverlapping trials, both studies demonstrated a significantly increased OS benefits, adding further validity to the findings.

Several limitations need to be mentioned in this analysis. First and most importantly, the application of formal meta-analytic methods to observational studies was controversial. One of the most important reasons for this is that the designs and populations of the studies were diverse and that these differences may influence the pooled estimates. However, as no
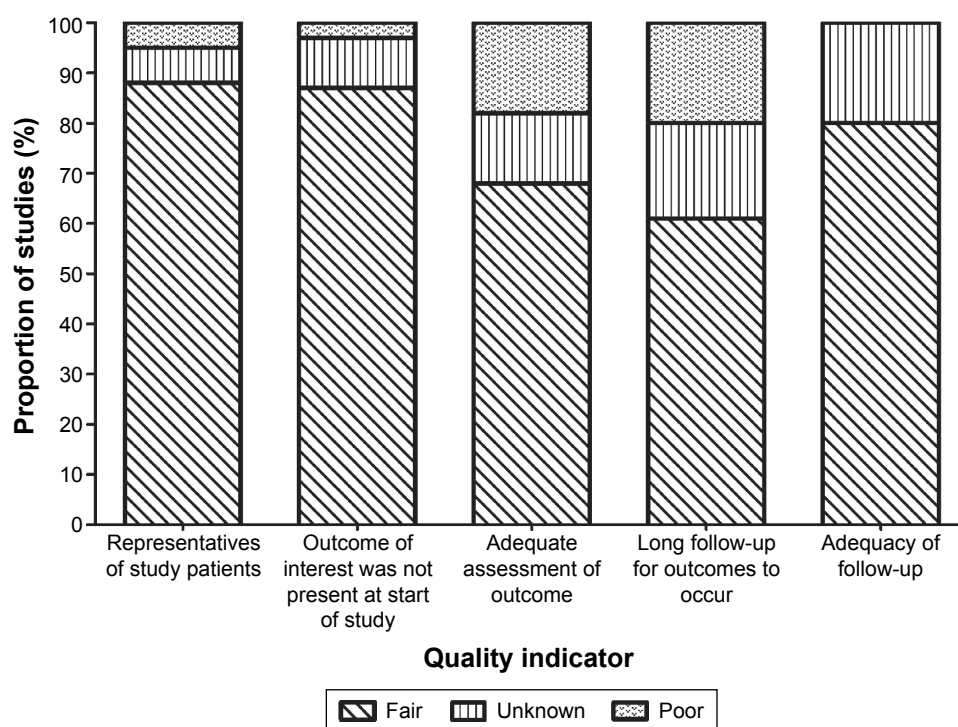
Figure 2 Selected methodological quality indicator.

Table 3 Comparison of primary outcomes for single agent versus combined chemotherapy

Groups	Cohorts (n)	Patients (n)	Events (95% CI)	I^2	Relative risk (95% CI)	P-value
ORR						
Single agent	19	709	15.3 (11.1–20.7)	55.5	1	
Combination	30	847	34.5 (29.7–39.6)	51.5	2.25 (1.60–3.18)	<0.001
DCR						
Single agent	13	545	50.9 (46.5–55.4)	71.8	1	
Combination	23	618	56.6 (52–60.1)	49.6	1.12 (1.01–1.25)	0.033
1-year OS						
Single agent	8	474	25.3 (15.9–37.7)	77.2	1	
Combination	20	644	38.5 (34.6–42.6)	6.0	1.52 (1.01–2.37)	0.03
2-year OS						
Single agent	5	379	12.3 (9.2–16.2)	23.3	1	
Combination	16	569	16.1 (13.1–19.6)	37.1	1.31 (0.92–1.85)	0.064

Note: $I^2 \geq 50\%$ suggests high heterogeneity across studies.
Abbreviations: ORR, objective response rate; DCR, disease control rate; OS, overall survival; CI, confidence interval.

head-to-head comparison data are available for combination chemotherapy versus single agent alone, a meta-analysis of observational studies is one of the few methods for assessing efficacy and toxicities.[59] Moreover, it represents the uncertainty surrounding the pooled estimates and is a valuable method to decide on whether more evidence is needed, which was a timely discussion topic with regard to salvage chemotherapy for advanced UC patients. Second, the study was a pooled analysis of primarily single-arm prospective studies and retrospective series, with a small number of patients included that might have overreported the benefit of preoperative treatments. The inclusion criteria also likely favor young, fit, and responder patients and a highly selected group of subjects with good prognostic indicators; all of these might cause potential selection bias. Third, we included UC patients treated with different combination or single agent chemotherapy for analysis, which would increase the clinical heterogeneity among included trials, which also made the interpretation of a meta-analysis more problematic. Additionally, we could not answer that which combination

Table 4 Comparison of higher than grade 3 toxic effect event rates for single agent versus combined chemotherapy

Toxicities	Included study	Events	Total	Events rate (95% CI)	I^2	RR (95% CI)	P-value
Hematologic toxicity							
Anemia							
Single agent	13	84	520	13.5 (9.2–19.4)	67.7	1	
Combination	26	110	765	14.6 (9.9–20.9)	49.7	1.08 (0.64–1.83)	0.39
Leukopenia							
Single agent	14	182	534	17.9 (9.2–32.1)	80.8	1	
Combination	26	327	724	45.5 (35.8–55.5)	88.0	2.54 (1.31–4.93)	<0.001
Thrombocytopenia							
Single agent	13	37	520	9.0 (6.6–12.1)	77.7	1	
Combination	26	118	724	15.9 (8.8–22.9)	40.3	1.77 (1.00–3.11)	0.024
Non-hematologic toxicity							
Nausea							
Single agent	9	16	399	5.6 (2.3–12.8)	61.1	1	
Combination	17	18	457	7.0 (4.6–10.3)	0	1.25 (0.48–3.23)	0.32
Vomiting							
Single agent	12	24	480	6.4 (3.5–11.6)	49.1	1	
Combination	16	12	419	6.0 (3.8–9.5)	0	0.93 (0.44–1.99)	0.43
Diarrhea							
Single agent	10	10	224	7.8 (4.4–13.5)	45.7	1	
Combination	12	11	327	4.9 (2.9–8.2)	0	0.63 (0.29–1.35)	0.12
Fatigue							
Single agent	9	74	372	17.7 (9.8–29.9)	70.3	1	
Combination	10	4	282	3.0 (1.5–6.1)	0	0.17 (0.07–0.42)	<0.001

Abbreviations: RR, relative risk; CI, confidence interval.

regimens would be the best choice. Finally, this meta-analysis only considered published literature, and lack of individual patient data restricted us from adjusting the treatment effect according to previous treatment and patient variables.

Conclusion

Currently available clinical evidence for advanced UC patients indicates that combined chemotherapy may be a more efficient regimen for previously treated UC patients, but with more frequencies of grade 3 and 4 myelosuppression toxicities compared with single agent. However, since the overall quantity and quality of data regarding salvage chemotherapy is poor, there might be risk of bias in comparisons between observation studies. No definite conclusions were attained from the results. As a result, prospective randomized studies, definitively comparing the survival and treatment toxicity between combined chemotherapy and single agent, are strongly recommended to clearly determine the role of combined chemotherapy as salvage treatment for previously treated UC patients.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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