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Management of Bladder Cancer
Current and Emerging Strategies

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Abstract

Cancer of the urinary bladder is the fifth most prevalent solid tumour in the US. Urothelial carcinoma is the most common form of bladder cancer, accounting for about 90% of cases. About 25% of patients with bladder cancer have advanced disease (muscle-invasive or metastatic disease) at presentation and are candidates for systemic chemotherapy. Urothelial carcinoma is a chemo-sensitive disease, with a high overall and complete response rate to combination chemotherapy. In the setting of muscle-invasive urothelial carcinoma, use of neoadjuvant chemotherapy is associated with overall survival benefit. The role of adjuvant chemotherapy in this setting is yet to be validated. In the setting of metastatic disease, use of cisplatin-based regimens improves survival. However, despite initial high response rates, the responses are typically not durable leading to recurrence and death in the vast majority of these patients. Currently, there is no standard second-line therapy for patients in whom first-line chemotherapy for metastatic disease has failed.

Many newer chemotherapeutic agents have shown modest activity in urothelial carcinoma. Improved understanding of molecular biology and pathogenesis of urothelial carcinoma has opened avenues for the use of molecularly targeted therapies, several of which are being tested in clinical trials. Currently, several novel drugs seem particularly promising including inhibitors of the epidermal growth factor receptor pathway, such as cetuximab, and inhibitors of tumour angiogenesis, such as bevacizumab and sunitinib. Development of reliable molecular predictive markers is expected to improve treatment decisions, therapy development and outcomes in urothelial carcinoma. Funding of and participation in clinical trials are key to advancing the care of urothelial cancer patients. Current and emerging strategies in the medical management of urothelial carcinoma are reviewed.

Cancer of the urinary bladder is the fifth most prevalent solid tumour in the US with an estimated 68 810 new cases and 14 070 deaths in 2008.[1] Transitional cell or urothelial carcinoma is the most common form of bladder cancer, accounting for about 90% of cases. Urothelial carcinoma can originate from the urothelial lining of the ureter, renal pelvis and urethra, and has a natural history similar to those arising from the urinary bladder. About 25% of patients with bladder cancer have advanced disease (muscle-invasive or metastatic disease) at presentation and are candidates for systemic chemotherapy. Urothelial carcinoma is a chemo-sensitive disease, with relatively high response rates (50–70%) to cisplatin-based regimens compared with other common solid tumours[2,3] In the setting of metastatic disease, despite initial high response rates, the responses to chemotherapy are typically not durable, leading to recurrence in the vast majority of these patients. Many newer chemotherapeutic agents have shown modest activity in urothelial carcinoma. Improved understanding of the molecular biology and pathogenesis of urothelial carcinoma has opened avenues for the use of molecularly targeted therapies, several of which are being tested in clinical trials. Development of reliable molecular predictive markers is expected to improve treatment decisions, therapy development and outcomes in urothelial carcinoma.

This article discusses current and emerging strategies in the medical management of urothelial carcinoma. MEDLINE via the PubMed database was searched for the following terms: 'urothelial carcinoma', 'transitional cell carcinoma', 'chemotherapy in adjuvant and neoadjuvant setting', 'first line chemotherapy', 'second line chemotherapy', 'salvage chemotherapy', 'newer agents' and 'novel therapeutic agents'.

1. Neoadjuvant and Adjuvant Chemotherapy in Urothelial Carcinoma

Fifty percent of patients with localized muscle-invasive urothelial carcinoma develop metastatic disease despite optimal surgical management,[4] suggesting the presence of micrometastasis in a significant proportion of patients at presentation. Given the chemosensitivity of urothelial carcinoma and the experience in other solid tumours, chemotherapy has been investigated in the neoadjuvant and adjuvant settings.

1.1 Neoadjuvant Chemotherapy

There are several advantages associated with the use of preoperative chemotherapy. These include the immediate treatment of microscopic metastasis, greater tolerability as a result of better performance status compared with postoperative patients, and *in vivo* assessment of the chemosensitivity of disease. In addition, the use of neoadjuvant chemotherapy for urothelial carcinoma has shown to be associated with survival benefit. Critics of neoadjuvant chemotherapy cite the delay in surgery[5] and the potential for

increased postoperative complications as disadvantages. In addition, there is the potential for overtreatment, as a proportion of patients with localized muscle-invasive urothelial carcinoma never develop metastatic disease.

In 2003, Grossman and colleagues[6] reported a phase III trial conducted by the South West Oncology Group. 317 patients with cT2 to cT4a urothelial carcinoma were randomized to three cycles of methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC), followed by cystectomy versus cystectomy alone. Notably, it took 11 years to complete accrual. Patients treated with M-VAC had improved median overall survival (77 vs 46 months; $p = 0.06$) and 5-year overall survival (57% vs 43%; $p = 0.06$). There was no apparent increase in post-operative morbidity or mortality. A survival benefit was observed in all subgroups and achieving complete pathological responses (P0) was a strong predictor of survival. Patients in the neoadjuvant group, compared with the cystectomy-only group, had a significantly higher rate of P0 status (38% vs 15%; $p < 0.001$) at the time of surgery. A larger, randomized phase III trial was conducted by the Medical Research Council, the European Organisation for Research and Treatment of Cancer (EORTC) and other investigators.[7] Patients with T2 grade 3 or T3/T4a disease were randomized to either local treatment ($n = 485$) with cystectomy or radiation versus three cycles of neoadjuvant cisplatin, methotrexate and vinblastine (CMV), followed by local treatment ($n = 491$). This study demonstrated a 3-year overall survival of 50% for the local treatment alone group versus 55.5% in the neoadjuvant chemotherapy group ($p = 0.075$). A study update following a median follow-up of 7 years was presented at the 2002 American Society of Clinical Oncology (ASCO) meeting. Patients treated with neoadjuvant chemotherapy had significantly superior survival versus those randomized to no chemotherapy ($p < 0.05$).[8]

In addition, several large meta-analyses have been performed.[9,10] Most recently in 2005, the Advanced Bladder Cancer Meta-Analysis Collaboration Group published a meta-analysis on 3005 individual patients. Data from 11 randomized trials compared the addition of a platinum-based chemotherapy with local treatment in invasive urothelial cell carcinoma.[9] After a median follow-up of 13 years, the meta-analysis demonstrated a significant survival benefit and an absolute improvement in 5-year overall survival of 5%, with neoadjuvant treatment (hazard ratio [HR] = 0.86; 95% CI 0.77, 0.95; $p = 0.003$).

Although the use of a gemcitabine and cisplatin (GC) regimen is associated with a similar survival to that of M-VAC in the setting of metastatic urothelial carcinoma, its role and benefit is yet to be established in the neoadjuvant setting. However, retrospective data suggest comparable effects. In a retrospective study of 96 patients with localized muscle-invasive urothelial carcinoma, treatment with a GC regimen ($n = 42$) was shown to result in a similar degree of tumour down-staging to that observed with an M-VAC regimen ($n = 56$).[10] The proportions of patients with complete response (pT0 stage) and with partial response (<pT2), were similar with GC and M-VAC regimens (26% vs 28% and 36% vs 35%, respectively). It is noteworthy that patients treated with a GC regimen in this study received four cycles of GC over 3 months and those treated with an M-VAC regimen received four cycles of M-VAC over 4 months. Despite increased dose intensity, the GC regimen was well tolerated and all patients were able to undergo radical cystectomy. Median number of days from the start of chemotherapy to radical cystectomy was 138 days (range 123–155) in the GC arm versus 125 days (range 89–175) in the M-VAC arm. In another retrospective study, 29 patients with localized muscle-invasive urothelial carcinoma were treated with neoadjuvant chemotherapy (GC, $n = 20$; M-VAC, $n = 4$; other regimens, $n = 5$).[11] Only two patients (7%) achieved a pathological complete response and 18 had non-organ-confined residual cancer with an overall median progression-free survival of 10.5 months. Notably, the interval from the time of diagnosis of muscle-invasive bladder cancer to radical cystectomy was considerably long (median 208 days, interquartile range, 149–327 days). The investigators attributed poor outcome with neoadjuvant chemotherapy, to either the use of non-M-VAC-based regimens or an excessive delay in

performing radical cystectomy and argued for the use of an M-VAC regimen in the neoadjuvant setting.[11]

In summary, the available data from the randomized studies support the use of three cycles of cisplatin-based combination chemotherapy; specifically M-VAC or CMV, as neoadjuvant therapy in muscle-invasive urothelial carcinoma in eligible patients. Prospective randomized trials have not demonstrated a disadvantage with regard to delay of local therapy or increased complications with local therapy.

1.2 Adjuvant Chemotherapy

Advantages of adjuvant chemotherapy include immediate local treatment without the delay associated with neoadjuvant chemotherapy and potentially better selection of high-risk patients. Disadvantages include delay in treatment of micrometastasis, relatively poorer performance status of postoperative patients, resulting in decreased tolerability to chemotherapy, and difficulty in evaluation of response because of the absence of tumour after surgery. In addition, data from adequately powered clinical trials to support adjuvant chemotherapy are lacking.

Skinner[12] reported a phase III trial of 91 patients with muscle-invasive urothelial carcinoma, comparing adjuvant chemotherapy to observation, after radical cystectomy and pelvic lymph node dissection. The difference in the 3-year survival was not statistically significant (66% vs 50%; $p = 0.09$). Moreover, the study has been criticized for having several methodological flaws. Stockle and colleagues[13,14] randomized 49 patients without evidence of residual tumour to chemotherapy (three cycles of M-VAC or methotrexate, vinblastine and cisplatin plus epirubicin [M-VEC]) or observation, after radical cystectomy. Although the improvement in the 5-year progression-free survival was statistically significant with the use of chemotherapy (59% vs 13%), this study was limited by a small sample size and early discontinuation. In addition, the investigators did not offer chemotherapy to patients in the observation group at the time of recurrence.

In a recent Italian randomized, multicentre, phase III trial of 192 patients with muscle-invasive urothelial carcinoma following radical cystectomy, patients were randomized to adjuvant chemotherapy with GC versus chemotherapy with GC at relapse. This trial was prematurely closed because of poor accrual. At a median follow-up of 32.5 months, there was no statistically significant improvement in disease-free or overall survival with adjuvant chemotherapy.[15] In October 2001, the EORTC started a large multicentre phase III trial, randomizing patients with muscle invasive urothelial carcinoma after radical cystectomy, to adjuvant chemotherapy versus chemotherapy at relapse. The investigators planned to enrol 660 patients. The study closed prematurely because of slow accrual.

The Advanced Bladder Cancer Meta-Analyses Collaboration reported on a meta-analysis of 491 individual patient data from six available randomized controlled trials. These trials compared local treatment, followed by adjuvant chemotherapy, with local treatment alone in patients with invasive bladder cancer.[16] Although the investigators reported a 25% relative reduction in the risk of death for chemotherapy compared with the control group, they observed serious methodological flaws such as suboptimal accrual of patients, patients not receiving allocated treatment, premature discontinuation of accrual and inappropriate analysis.

In summary, at this time there is insufficient evidence to support the routine use of adjuvant chemotherapy in the treatment of muscle-invasive urothelial carcinoma. However, clinical decisions regarding adjuvant therapy can be made individually, based on the risk of relapse and the feasibility of administering therapy postoperatively.

2. Chemotherapy in the Setting of Metastatic Disease

2.1 First-Line Chemotherapy

2.1.1 Methotrexate, Vinblastine, Doxorubicin and Cisplatin (M-VAC) Regimen

In a prospective, randomized, multi-institutional trial, Loehrer and colleagues[17] compared M-VAC

Table I. Selected randomized studies comparing methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) with other cisplatin-based regimens as first-line therapy in patients with metastatic urothelial carcinoma

Study	Chemotherapy	Patients	RR (%)	Median OS (mo)	p-Value
Logothetis et al.[2]	M-VAC	110	65	12.6	<0.001
	CISCA		55	10.0	
Loehrer et al.[17]	M-VAC	255	36	12.5	<0.05
	Cisplatin		11	8.2	
von der Maase et al.[3,19]	M-VAC	405	46	15.2	NS
	GC		49	14.0	
Siefker-Radtke et al.[20]	M-VAC	172	59	12.5	NS
	FIP		42	12.5	
Sternberg et al.[21,22]	M-VAC	263	50	14.9	NS
	HD M-VAC + GCSF		64	15.1	
Bamias et al.[23]	M-VAC	220	54	14.2	<0.05
	DC + GCSF		37	9.3	

CISCA = cisplatin, cyclophosphamide and doxorubicin (Adriamycin); **DC** = docetaxel and cisplatin; **FIP** = fluorouracil, interferon-α-2b and cisplatin; **GC** = gemcitabine and cisplatin; **GCSF** = granulocyte colony stimulating factor; **HD** = high-dose; **NS** = not significant; **OS** = overall survival; **RR** = response rate.

(methotrexate 30 mg/m^2 on days 1, 15 and 22; vinblastine 3 mg/m^2 on days 2, 15 and 22; doxorubicin 30 mg/m^2 on day 2 and cisplatin 70 mg/m^2 on day 2) with cisplatin alone (70 mg/m^2) in 269 patients with advanced urothelial carcinoma. Cycles were repeated every 28 days, until tumour progression or for a maximum of six cycles. The M-VAC regimen, when compared with single-agent cisplatin, demonstrated significantly better response rates (39% vs 12%; $p < 0.0001$), progression-free survival (10.0 vs 4.3 months) and overall survival (12.5 vs 8.2 months). It should be noted that the incidences of high-grade granulocytopenia, neutropenic fever, sepsis, mucositis, nausea and vomiting were significantly higher in patients treated with M-VAC. Performance status was the most important factor with respect to response to therapy and survival. Additional prognostic factors were prior weight loss and sites of metastatic disease. The patients with the most favourable prognostic features (i.e. Karnofsky performance status >90, no weight loss and no pulmonary, hepatic or osseous metastases) had a median survival of 18.2 months, while those with the least favourable prognostic features (i.e. Karnofsky performance status <80, weight loss and/or pulmonary, hepatic and/or osseous metastases) had a median survival of 4.4 months. In an updated report by Saxman and colleagues,[18] survival in the M-VAC arm continued to be superior to cisplatin ($p = 0.00015$). Only 3.7% of the patients randomized to M-VAC were alive and continuously disease-free at 6 years.

In an effort to improve efficacy of M-VAC, several cisplatin-based combination regimens have been compared with M-VAC and were not found to be superior to M-VAC with regard to survival (table I).

2.1.2 Gemcitabine and Cisplatin Regimen

Multiple phase II studies have suggested that a combination of gemcitabine and cisplatin is active in metastatic urothelial cancer in chemotherapy-naive patients, with an acceptable clinical safety profile.[24-26] This led to a large, randomized, phase III, multicentre study comparing GC with M-VAC, in patients with locally advanced or metastatic urothelial carcinoma. In this landmark study, Von der Masse and colleagues[24] randomized 405 patients to GC (gemcitabine 1000 mg/m^2 days 1, 8 and 15; cisplatin 70 mg/m^2 day 2) or standard M-VAC, every 28 days for a maximum of six cycles. Overall survival, time to progression and response rates were similar for both arms. More GC patients completed six cycles of therapy with fewer dose adjustments. More GC than M-VAC patients had grade 3 or 4 anaemia and thrombocytopenia.

However, more M-VAC patients, compared with GC patients, had grade 3 or 4 neutropenia, neutropenic fever, neutropenic sepsis, and grade 3 or 4 mucositis and alopecia.

In summary, GC provided a similar survival advantage to M-VAC, with a better safety profile and tolerability. In an updated report, long-term overall and progression-free survival after treatment with GC or M-VAC were similar, thus strengthening the role of GC as a first-line chemotherapy in patients with locally advanced or metastatic urothelial carcinoma.[19]

2.1.3 Other Non-Cisplatin or Non-Platinum Drug Combinations

Trials with carboplatin-based regimens in patients with adequate renal function have shown inferior complete response rates and shorter median survival compared with cisplatin-based regimens (table II). Similarly, non-platinum regimens have been unsuccessful in matching the response rates and median survival seen with cisplatin-based regimens (table II). Although there are no large phase III trials, the phase II data collectively would suggest that carboplatin-based and non-platinum-based regimens cannot be routinely recommended for cisplatin-eligible patients.

2.1.4 Three-Drug Combination Regimens Combinations

With the goal of improving response rates and median survival, various combinations of three drugs (triplets) have been studied in several phase II studies (table III). Based on these results, the EORTC conducted a phase III trial in which 627 patients with previously untreated metastatic bladder cancer were randomly assigned to GC or to triplet GC plus paclitaxel (PCG).[41] The overall response rates and complete responses were higher with PCG (57% and 15%) than with GC (46% and 10%), but the overall survival with PCG (15.7 months) was not significantly better than with GC (12.8 months) [table III]. However, in an unplanned subgroup analysis of 512 patients with the bladder as the primary origin of urothelial cancer, the overall survival with PCG was significantly higher than that of GC ($p = 0.03$). There was a higher incidence of grade 3 or 4 neutropenia with the PCG regimen

Table II. Selected trials of carboplatin and non-platinum-based drug regimens as first-line therapy in patients with metastatic urothelial carcinoma

Study	Chemotherapy	Patients	RR (%)	Median OS (mo)	p-Value
Bellmunt et al.[27]	M-VAC	47	52	16	<0.05
	M-CAVI		39	9	
Petrioli et al.[28]	M-VEC	57	71	NR	<0.05
	M-VECa		41		
Dreicer et al.[29]	M-VAC	85	36	15.4	NS
	CP		28	13.8	
Dogliotti et al[30]	GC	110	49	12.8	NS
	GCa		40	9.8	
Li et al.[31]	PG[a]	36	69	15.8	
Meluch et al.[32]	PG	54	54	14.4	
Parameswaran et al.[33]	PG	24	61	NR	
Gitlitz et al.[34]	DG	27	33	12	
Ardavanis et al.[35]	DG	31	52	15	

a High incidence of pulmonary toxicity.

CP = carboplatin and paclitaxel; **DG** = gemcitabine and docetaxel; **GC** = gemcitabine and cisplatin; **GCa** = gemcitabine and carboplatin; **M-CAVI** = methotrexate, carboplatin and vinblastine; **M-VAC** = methotrexate, vinblastine, doxorubicin and cisplatin; **M-VEC** = methotrexate, vinblastine, epirubicin and cisplatin; **M-VECa** = methotrexate, vinblastine, epirubicin and carboplatin; **NS** = not significant; **NR** = not reported; **PG** = paclitaxel and gemcitabine; **OS** = overall survival; **RR** = response rate.

Table III. Selected trials of three-drug regimens as first-line therapy in patients with metastatic urothelial carcinoma

Study	Chemotherapy	Patients	RR (%)	Median OS (mo)	p-Value
Bellmunt et al.[36]	PCG	58	76	15.6	
Bajorin et al.[37]	IPC	44	68	20	
Hussain et al.[38]	PCaG	49	68	14.7	
Pectasides et al.[39]	DCG	35	66	15.5	
Lara et al.[40]	PCM	25	57	18	
Bellmunt et al.[41]	PCG	627	57	15.7	NS
	GC		46	12.8	

DCG = docetaxel, gemcitabine and cisplatin; **GC** = gemcitabine and cisplatin; **IPC** = ifosfamide, paclitaxel and cisplatin; **PCaG** = paclitaxel, carboplatin and gemcitabine; **NS** = not significant; **OS** = overall survival; **PCG** = paclitaxel, cisplatin and gemcitabine; **PCM** = paclitaxel, gemcitabine and methotrexate; **RR** = response rate.

and higher incidence of grade 3 or 4 thrombocytopenia with the GC regimen. The death rate due to toxicity was the same (two patients each arm).

2.2 Second-Line Therapy

Most patients with advanced urothelial carcinoma eventually have disease progression or recurrence after treatment with first-line chemotherapy. There is no standard salvage chemotherapy regimen for this group of patients. Several agents have shown modest responses in this setting including docetaxel (overall response rate [RR] 13%),[42] paclitaxel (RR 7–10%),[43,44] gemcitabine (RR 22.5%),[45] ifosfamide (RR 20%)[46] and combination gemcitabine-paclitaxel (RR 60%).[47]

In addition, several newer agents have been studied in the treatment of advanced urothelial carcinoma. Epothilones, vinflunine and pemetrexed are among the newer agents that have been shown to have modest activity in clinical trials.

2.2.1 Ixabepilone

Drugs that target microtubules are commonly used anticancer therapies. Epothilones have emerged as a new class of microtubule-targeting drugs, which by stabilizing microtubules, lead to microtubule bundling, formation of multipolar spindles and mitotic arrest.[48] The epothilone B analogue ixabepilone (BMS-247550) has been investigated by Dreicer and colleagues[49] in a phase II trial of 45 previously treated patients with advanced urothelial carcinoma. The overall response rate and median survival were 12% and 8 months, respectively, with a moderate toxicity profile. Granulocytopenia, fatigue and sensory neuropathy were the most common adverse effects.

2.2.2 Vinflunine

Vinflunine is a novel vinca alkaloid that targets microtubules. In a phase II trial by Culine and colleagues,[50] 51 patients with advanced urothelial carcinoma, who were previously treated with a first-line platinum-containing regimen, were treated with vinflunine. The overall response rate and median overall survival were 18% and 6.6 months, respectively. In a larger phase II trial of vinflunine in 151 patients with platinum refractory advanced urothelial carcinoma, the overall response rate and median overall survival were 15% and 7.9 months, respectively.[51] In a randomized phase III trial of 370 patients with previously treated advanced urothelial carcinoma, Bellmunt and colleagues[52] compared vinflunine plus best supportive care (n = 253) with best supportive care alone (n = 117). The preliminary results of this study were presented at the ASCO annual meeting in June 2008. Treatment with vinflunine was associated with an overall response rate of 9% and a statistically nonsignificant increase in survival (6.9 vs 4.6 months; HR 0.88; 95% CI 0.69, 1.12). However, a planned multivariate analysis adjusting for prognostic factors showed a statistically significant effect of vinflunine on overall survival (6.9 vs 4.3 months; p = 0.036). The results of this study indicated that vinflunine has a very modest level of activity, as reflected by a 2-month survival improvement in the eligible population; durable responses in those who responded, despite a low response rate

(the duration was 7.4 months); and an improvement in progression-free survival, from 1.5 to 3 months.

2.2.3 Pemetrexed

Pemetrexed is a multitargeted antifolate agent that works by inhibiting multiple enzymes involved in DNA synthesis. In a small phase II study of 13 patients with advanced urothelial carcinoma who had relapsed after receiving perioperative chemotherapy or first-line chemotherapy for metastatic disease, treatment with pemetrexed resulted in an overall response rate of 8%.[53] In a phase II study of 47 patients with previously treated advanced urothelial carcinoma (previous treatment included one prior chemotherapy regimen for advanced urothelial carcinoma, as well as adjuvant or neoadjuvant chemotherapy, within 1 year of accrual). The overall response rate, complete response rate and median overall survival were 28%, 6% and 9.6 months, respectively.[54]

2.2.4 Summary

With the exception of vinflunine,[52] none of the agents used in second-line therapy have undergone testing in a randomized study. At present, it is reasonable to consider clinical trial participation as viable first option for patients with urothelial carcinoma in whom frontline chemotherapy for advanced-stage disease has failed.

2.3 Novel Biological Agents

Advancements in molecular biology have led to improved understanding of the tumour biology of urothelial carcinoma. Like several other cancers, pathogenesis of urothelial carcinoma is associated with aberrancy of biological pathways involved in cellular proliferation, tumour angiogenesis, apoptosis, and of tumour suppressor genes and regulatory transcription factors. Among these, epidermal growth factor receptor (EGFR) and angiogenesis pathways are particularly important because relatively effective drugs targeting these pathways have recently become available.

Human EGFRs are involved in signal transduction pathways, resulting in proliferation, cell survival, angiogenesis and metastasis.[55] The EGFR family is comprised of four closely related receptors: ErbB1(EGFR, HER1), ErbB2 (HER2/neu), ErbB3 (HER3) and ErbB4 (HER4). Over expression of ErbB receptors has prognostic and therapeutic significance in various malignancies, including bladder cancer.[56] In urothelial carcinoma, the level of EGFR expression has been directly correlated with higher tumour grade and stage, disease progression, recurrence and poorer prognosis.[57-60] In multivariate analysis, the presence of EGFR expression in urothelial carcinoma has been shown to be an independent predictor of invasive disease, stage progression, inferior survival and poor outcome.[61-63] Similarly important in the biology of urothelial carcinoma is the role of tumour angiogenesis. Vascular endothelial growth factor (VEGF) plays a pivotal role in tumour angiogenesis, a process critical for tumour development, invasion and metastasis.[64] Higher levels of VEGF in urine predict increased risk of recurrence in patients with superficial urothelial carcinoma.[64] VEGF gene expression level has been found to be strongly related with disease-specific survival in patients with locally advanced urothelial carcinoma.[65] Quantification of angiogenesis can be performed by immunohistochemical staining of endothelial cells and by measuring the mean tumour vascular density (MVD). MVD predicts subsequent muscle invasion in superficial bladder cancer,[66] and has been shown to directly correlate with tumour grade, stage and poor prognosis in bladder cancer.[67] Agents targeting several other biological pathways involved in the pathogenesis of urothelial carcinoma are also available and some of the promising ones are described later in the text.

2.3.1 Inhibitors of the Epidermal Growth Factor Receptor Pathway

Encouraging results were obtained in preclinical models using the EGFR tyrosine kinase inhibitor, geftinib and lapatinib.[68,69] In recent years, several agents targeting the EGFR signalling pathway have been developed. These include monoclonal antibodies against the extracellular domain of the receptor, as well as small molecule

tyrosine kinase inhibitors that inhibit phosphorylation of the intracellular tyrosine kinase domain of the EGFR receptors.

Cetuximab

Cetuximab is a recombinant, human/murine chimeric monoclonal antibody that binds specifically to the extracellular domain of the human EGFR/HER1, which has been approved by the US FDA for the treatment of colorectal and head-and-neck cancer. Treatment with cetuximab results in EGFR inhibition and down-regulation, resulting in inhibition of the downstream signalling pathways of the EGFR. Based on the preclinical and clinical data that demonstrate the importance of the epidermal growth factor pathway in urothelial carcinoma, cetuximab efficacy in preclinical urothelial cancer models, and the enhanced clinical efficacy of combining cetuximab with chemotherapy in advanced colorectal and head-and-neck cancers, a randomized, open label, phase II trial is currently evaluating the efficacy and safety of the addition of cetuximab to GC in patients with locally advanced and metastatic urothelial carcinoma.[70]

Geftinib

Geftinib is an oral EGFR tyrosine kinase inhibitor. In a phase II study, Philips and colleagues[71] treated 27 treatment-naive patients with advanced urothelial carcinoma with GC plus geftinib. This regimen was associated with excessive toxicity. The overall response rate and median overall survival were 36% and 11.1 months, respectively.[71]

Transtuzumab

HER2/neu (c-erb-B2) is over expressed in approximately 30% of breast cancers, and is associated with a poor prognosis.[72] Trastuzumab, a humanized monoclonal antibody that binds to HER2/neu, is approved for treatment of breast cancer with amplified HER2/neu receptor. In urothelial carcinoma, the amplification of HER2/neu has been shown to correlate with the grade and stage of urothelial carcinoma. Patients with grade 3 tumours and concomitant HER2/neu amplification had a worse prognosis with multivariate analysis, indicating grade and HER2/neu amplification to be independent prognostic factors.[73] In a series of 80 cases of muscle-invasive urothelial carcinoma of the bladder, 28% cases of primary tumour and 53% cases of lymph node metastasis were HER-2/neu-positive. Although commonly over expressed, median survival did not correlate with HER2/neu-positivity (33 months for positive cases vs 50 months for negative cases, $p = 0.46$).[74] In a phase II, multicentre study, trastuzumab was combined with a three-drug regimen of paclitaxel, carboplatin and gemcitabine (TPCG) for the first-line treatment of patients with HER-2/neu–positive metastatic urothelial cancer.[75] HER-2/neu over expression was assessed by immunohistochemistry (IHC) of the primary or metastatic tumour, gene amplification and serum HER-2/neu extracellular domain assay. Of 109 patients screened, 57 met the criteria for HER-2/neu positivity (49% positive by IHC). HER-2/neu-positive patients demonstrated an increased number of metastases compared with HER-2/neu-negative patients (two vs one; $p = 0.014$); a greater probability of having two or more metastatic sites (51% vs 31%; $p = 0.051$) and a trend toward more liver and bone metastases. Of these 57 patients, 44 were treated with TPCG. The overall response rate and median overall survival were 70% and 14.1 months, respectively. Although the response rate and median survival were similar to those treated with PCG,[38] patients treated with TPCG had higher visceral sites of metastases (liver, lung or bone), a known independent poor prognostic factor in urothelial carcinoma.[76]

2.3.2 Inhibitors of Angiogenesis

Agents targeting the VEGF signalling pathway available for clinic use include bevacizumab, sunitinib and sorafenib. While bevacizumab is a monoclonal antibody, sunitinib and sorafenib are small-molecule, multi-targeted tyrosine kinase inhibitors, with significant inhibitory activity on VEGF tyrosine kinase.

Bevacizumab

HOG (Hoosier Oncology Group) has completed a phase II study using bevacizumab in combination with GC as first-line therapy in

metastatic urothelial carcinoma with results expected in the near future. CALGB (Cancer and Leukemia Group B) has planned a phase III randomized study of GC with and without bevacizumab as first-line therapy.

Sunitinib

A preclinical study has shown activity for sunitinib, both as a single agent and combined with cisplatin in urothelial carcinoma cell lines.[77] In a phase II study, Gallagher and colleagues[78] treated 45 patients with previously treated advanced urothelial carcinoma with sunitinib. Three of 41 patients with evaluable disease had a partial response. A phase II trial is currently ongoing and is investigating the role of sunitinib as maintenance therapy in patients with advanced urothelial cancer.[79,80]

2.3.3 Other Pathways and Agents

Several other biological agents have been or are being investigated in the treatment of urothelial carcinoma, including histone deacetylase inhibitors, farnesyl transferase inhibitors and proteasome inhibitors.

Histone deacetylase inhibitors modify histone acetylation. Histone acetylation affects chromatin structure and gene expression. The degree of acetylation is determined by the opposing activities of histone acetyltransferase and histone deacetylase (HDAC). HDACs have been shown to be involved in malignant transformation by mediating the function of transcription factors.[81] Inhibitors of HDAC activity such as suberoylanilide hydroxamic acid (SAHA) induce differentiation, growth arrest and/or apoptosis of transformed cells in culture, and inhibit tumour growth in animals.[82] In phase I studies, oral and intravenous SAHA were well tolerated, inhibited the biological target *in vivo* and had a broad range of antitumour activity.[83,84] A novel HDAC inhibitor, belinostat, has been shown to suppress bladder cancer cell growth *in vitro* and in mice.[85] Romidepsin (depsipeptide) is another HDAC inhibitor and was found to be safe in a phase I study of patients with refractory tumours.[86] Several phase II studies of HDAC inhibitors in urothelial carcinoma are currently ongoing.

Farnesyl transferase is responsible for a posttranslational modification (farnesylation). Farnesylation is required for the function of a number of proteins involved in signal transduction pathways. Among these proteins are Ras proteins that transmit signals from cell surface receptors and mediate a range of cellular effects such as cellular proliferation, survival and angiogenesis.[87] Farnesyl transferase inhibitors include tipifarnib and lonafarnib. In many preclinical series of urothelial carcinoma, Ras mutations have been found to be prevalent, albeit with varying frequencies.[88-90] However, in several phase II studies in patients with urothelial carcinoma, farnesyl transferase inhibitors only resulted in very modest responses.[91-93]

Proteasome inhibitors such as bortezomib inhibit proteasomes. The 26S ubiquitin-proteosome is present in both the cytoplasm and the nucleus of all eukaryotic cells, and modulates both the levels and functions of proteins involved in cell cycle progression, differentiation, apoptosis and adhesion to the microenvironment.[94,95] In two phase II studies, no responses were noted when previously treated patients with urothelial carcinoma were treated with bortezomib.[96,97]

2.4 Chemotherapy for Cisplatin-Ineligible Patients

The adverse effect profile of cisplatin makes it difficult for certain populations to tolerate therapy with cisplatin. These include elderly patients or those with poor performance status, impaired cardiac or renal function (creatinine clearance of ≤50–60 mL/min) or significant co-morbidities (significant neuropathy or peripheral vascular disease). Although advanced age by itself should not preclude an otherwise healthy individual from being treated with cisplatin-based chemotherapy,[98] proper clinical judgment must be exercised in deciding on therapy in elderly patients, taking into account the objectives of treatment, as well as the benefit-risk ratio. Chronological age alone does not always predict tolerance to chemotherapy. Among individuals of similar age, there is a wide variation in tolerability to chemotherapy. In addition to co-morbidities, aging is

Table IV. Selected non-cisplatin-based regimens studied in cisplatin-ineligible patients with metastatic urothelial carcinoma

Study	Chemotherapy	Patients	RR (%)	Median OS (mo)	p-Value
Linardou et al.[103]	GCa	56	36	7.2	
Bellmunt et al.[104]	GCa	16	44	NR	
De Santis et al.[105]	GCa	178	42	NR	NR
	M-CAVI[a]		30		
Ricci et al.[106]	GE	38	39.5	8	
Turkolmez et al.[107]	GV	31	48	15	

a Phase III ongoing.

GCa = gemcitabine and carboplatin; **GE** = gemcitabine plus epirubicin; **GV** = gemcitabine and vinorelbine; **M-CAVI** = methotrexate, carboplatin and vinblastine; **NR** = not reported; **OS** = overall survival; **RR** = response rate.

also associated with changes in normal physiology, which have the potential to impact on the outcome of chemotherapy. Although estimating performance status is helpful, comprehensive geriatric assessment tools have been developed for elderly patients with cancer.[99,100] These tools consider not only the existing co-morbidities, but also normally occurring physiological changes in an elderly person. More frequent use of geriatric assessment tools are expected to improve treatment outcome and quality of life in elderly patients. In addition, the use of geriatric assessment tools have been shown to be feasible[101] and may not be associated with an increased cost of medical care.[102]

Currently, no phase III trials have been performed to validate the clinical benefit in terms of survival of a non-cisplatin-based combination compared with a single agent in cisplatin-ineligible patients. However, the inability to receive cisplatin is not necessarily an automatic exclusion from administration of other combination therapy with the intent of palliation. The medical decision should be individualized based on a patient's performance status and organ function, etc. (table IV).

3. Conclusions

The standard of care for off-protocol first-line therapy of advanced urothelial carcinoma patients who are candidates for cisplatin therapy is GC or M-VAC, with a median overall survival of 14–16 months. GC has become the community standard based on its more convenient schedule, as well as better overall toxicity profile. Both of these therapies are non curative and better treatments are crucially needed. Most patients with metastatic urothelial carcinoma following treatment with first-line therapy eventually develop disease recurrence and have a poor long-term survival. There is no current standard of care for the treatment of urothelial carcinoma in the second-line setting.

Further emphasis on drug development research is needed for the discovery of more effective systemic therapies. Several novel drugs seem particularly promising including inhibitors of the EGFR pathway, such as cetuximab, and inhibitors of tumour angiogenesis, such as bevacizumab and sunitinib. These are currently being tested in clinical trials. Development of molecular predictive markers will help to personalize therapy of urothelial cancer and is expected to improve responses to chemotherapeutic and biological agents.

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