Optimizing management of advanced urothelial carcinoma: A review of emerging therapies and biomarker-driven patient selection

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Abstract

Introduction: Advanced urothelial carcinoma has been challenging to treat due to limited treatment options, poor response rates, and poor long-term survival. New treatment options hold the promise of improved outcomes for these patients.

Methods: A multidisciplinary working group drafted a management algorithm for advanced urothelial carcinoma using "consensus development conference" methodology. A targeted literature search identified new and emerging treatments for inclusion in the management algorithm. Published clinical data were considered during the algorithm development process, as well as the risks and benefits of the treatment options. Biomarkers to guide patient selection in clinical trials for new treatments were incorporated into the algorithm.

Results: The advanced urothelial carcinoma management algorithm includes newly approved first-line anti-programmed death receptor-1 (PD1)/ programmed death-ligand 1 (PD-L1) therapies, a newly approved anti-fibroblast growth factor receptors (FGFR) therapy, and an emerging anti-Nectin 4 therapy, which have had encouraging results in phase 2 trials for second-line and third-line therapy, respectively. This algorithm also incorporates suggestions for biomarker testing of PD-L1 expression and FGFR gene alterations.

Conclusions: Newly approved and emerging therapies are starting to cover an unmet need for more treatment options, better response rates, and improved overall survival in advanced urothelial carcinoma. The management algorithm provides guidance on how to incorporate these new options, and their associated biomarkers, into clinical practice.

Introduction

Urothelial carcinoma is a significant cause of cancer-related morbidity and mortality in Canada; it is the fourth most commonly diagnosed cancer in men and is expected to account for 11 800 new cases and 2500 deaths in 2019.[1] About 25% of patients present with muscle-invasive disease, are at high risk for recurrence and metastasis, and have guarded long-term survival rates of 36% for regional disease and 5% for metastatic disease.[2,3] Platinum-based chemotherapy has traditionally been the first-line treatment for unresectable locally advanced or metastatic urothelial carcinoma; however, the median overall survival (OS) with gemcitabine and cisplatin is only 12–15 months, and a five-year survival of only 15%.[4-6]

Few therapeutic options were available for second-line metastatic urothelial carcinoma until recently. Between 2017 and early 2018, four immune checkpoint inhibitors — pembrolizumab, atezolizumab, durvalumab, and avelumab — were approved in Canada for patients with locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. Pembrolizumab is associated with an approximately three-month survival advantage over chemotherapy in the second-line setting, with a median OS of 10.3 months compared to 7.4 months on chemotherapy (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.59–0.91; p=0.002). Response rates for immune checkpoint inhibitors in general are relatively low but durable; approximately 13–24% of patients respond.[7-12]

New therapeutic options are on the horizon, with positive phase 2 clinical trial results published recently for

erdafitinib and enfortumab vedotin (EV).[13,14] Erdafitinib is a tyrosine kinase inhibitor of fibroblast growth factor receptors 1 to 4 (FGFR 1–4). Mutations and fusions in FGFR 2 and 3 are found in approximately 20% of patients with invasive urothelial carcinoma and result in constitutive FGFR signalling that can lead to carcinogenesis.[15,16] Erdafitinib received Breakthrough Therapy designation from the U.S. Food and Drug Administration (FDA) in March 2018, accelerated approval from the FDA in April 2019, and Notice of Compliance with Condition to complete phase 3 studies from Health Canada in October 2019, for the treatment of adults with locally advanced or metastatic urothelial carcinoma, which is characterized by susceptible FGFR 2 or 3 genetic alterations, and who have progressed after at least one line of platinum-containing chemotherapy. EV is an emerging therapy that received Breakthrough Therapy designation from the FDA in March 2018 and was FDA-approved in December 2019 for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. It is an antibody-drug conjugate consisting of a monoclonal antibody directed against Nectin-4, conjugated to a microtubule-disrupting agent.[17] This is the first agent targeting Nectin-4, which is expressed on many solid tumors, including urothelial carcinoma.

With the introduction of these new therapeutics comes the urgent need for biomarker testing to help guide treatment selection and sequencing of drugs. In first-line treatment, cisplatin-ineligible but carboplatin-eligible patients may be selected for anti-PD-L1 therapy rather than carboplatin-based chemotherapy by testing tumor tissue for PD-L1 expression levels.[18] FGFR-targeted therapy will be administered only to patients with altered FGFR2 or FGFR3 in tumor tissue. Nectin-4 is expressed on virtually all advanced urothelial carcinoma so that use of EV is not dependent on a biomarker.

With new advances in treatment options in the metastatic setting and increasing use of biomarker-driven patient selection, guidance is required to help clinicians understand how to incorporate new treatment options and required biomarker testing to optimize management of urothelial carcinoma. A national, multidisciplinary working group was convened to develop a management algorithm and practice guidance to help clinicians understand the potential place in therapy for new agents and optimal use and timing of biomarker testing.

Methods

Algorithm development

A multidisciplinary, national working group was formed to develop a management algorithm for advanced urothelial carcinoma. This group had pan-Canadian representation and included medical oncologists, urologic oncologists, pathologists, and laboratory medicine specialists. The working group began by reviewing an established bladder cancer care pathway[19] and subsequently incorporated emerging treatments and predictive biomarkers according to scientific evidence and anticipated approvals. Emerging treatments were included if phase 2 clinical trial data had been published by July 2019 or an Investigational New Drug (IND) submission had been posted on the Health Canada website by July 2019 (anticipated approval by July 2020). Inclusion of predictive biomarkers was restricted to biomarkers that had been used to guide patient selection in clinical trials for emerging treatments as described above. The group discussion considered all the published evidence available supporting the new therapies, as well as their benefits and risks for patients. In areas with limited published evidence, expert opinion was considered along with the published evidence, and the level of evidence used has been described throughout. The algorithm assumes that patient inclusion in clinical trials and best supportive care are options at any stage of treatment for advanced bladder cancer. Treatment choices supported by phase 3 data were preferred where possible, although the group supported a model that allows for clinical judgement to be used to determine the best course of action for an individual patient. The working group was divided into two subgroups — treatment and testing — to separately draft management algorithms in an iterative fashion through initial virtual meetings. The treatment subgroup focused on optimal use of current and emerging treatments, while the testing subgroup focused on the integration of predictive biomarkers. The full group was subsequently assembled to review both algorithms and develop a final management algorithm using a consensus development conference methodology.[20]

Literature search

A targeted literature search was performed to identify primary reports of phase 2 or 3 clinical trials of therapies for unresectable locally advanced or metastatic urothelial carcinoma. In order to update a previously developed management algorithm, the literature search focused on publications that appeared in MEDLINE between January 1, 2017 (the year prior to publication of a previous management algorithm[18]) and July 31, 2019. Treatments that had favorable efficacy and safety profiles from full clinical trial analyses were included

in the new management algorithm; treatments that only had interim or preliminary results published were excluded.

Results and discussion

The management of urothelial carcinoma is a rapidly evolving area. Guidelines for currently approved therapies were recently published;[21] however, since that publication, additional therapies have already been approved for new indications within the metastatic setting,[18] and further new therapies are expected to be approved over the next year.

Literature search results

The targeted literature search revealed that pembrolizumab and atezolizumab published phase 3 trials in the second-line setting and phase 2 trials in the first-line setting for cisplatin-ineligible patients.[7-12] Additional data in the second-line setting have been published with avelumab, durvalumab, and erdafitinib.[10,12,13] Phase 2 data with EV data in the third-line setting have also been published.[14] Although phase 2 data were also published with nivolumab in the second-line setting, it was excluded from consideration for inclusion in the algorithm because, unlike the other second-line immunotherapy agents, it is not approved by Health Canada.[22] Infigratinib (BGJ398) is a fibroblast growth factor receptor inhibitor that has been shown to have encouraging efficacy in a phase 1 expansion study (NCT01004224) in 67 patients with advanced urothelial carcinoma, but it is not included in the algorithm because no results are available from phase 2 or phase 3 studies. Rogaratinib is at a similar stage of clinical development.[23]

Summary of clinical data for new and emerging therapies

KEYNOTE-052 and IMvigor-210 examined pembrolizumab and atezolizumab, respectively, in patients ineligible for cisplatin chemotherapy (Table 1).[7,8] The objective response rate (ORR) was 24% for pembrolizumab and 23% for atezolizumab. Responses were seen regardless of PD-L1 expression levels, although an increased ORR was observed in patients with high PD-L1 expression when treated with pembrolizumab. The median duration of response was not reached in either study, although the available data indicated that the duration of responses was longer than for chemotherapy. The safety profiles of both agents were acceptable, with reversible immune-mediated toxicity occurring in about 10–20% of patients.[18] The initial FDA approvals for these agents were subsequently revised based on unpublished early review of data from the respective ongoing phase 3 trials, which suggested that patients with low levels of PD-L1 expression had decreased survival with pembrolizumab or atezolizumab monotherapy compared to patients receiving platinum-based chemotherapy. Subsequent publication of results with first-line atezolizumab demonstrated that the OS curves converged after approximately 12 months.[24] The FDA approvals for pembrolizumab and atezolizumab, and the Health Canada approval for pembrolizumab, are now restricted to patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 expression levels, and for patients who are cisplatin-ineligible but eligible for carboplatin chemotherapy with high PD-L1 expression levels.[18] Four immunotherapies have been approved in Canada as second-line therapy. Of these, pembrolizumab and atezolizmab are currently the only two with published phase 3 trial results, KEYNOTE-045 and IMvigor-211, respectively. Of these two trials, KEYNOTE-045 was the only one to demonstrate a significant difference in OS for immunotherapy compared to chemotherapy, by approximately three months.[9] This survival benefit was seen in the total population, not selected by PD-L1 expression level, as well as in the high PD-L1-expression subgroup. In addition, immunotherapy had a better safety profile than chemotherapy in both trials.[9,11] For the four available second-line immunotherapy agents, ORR varied from 13–21% (Table 2). Results from phase 2 clinical trials for these agents varied in whether PD-L1/PD-1 expression levels predicted for increased efficacy, although all four therapies did show efficacy regardless of expression levels.[9-12]

Phase 2 clinical trials reported objective response rates of 40% for erdafitinib and 44% for EV,[13,14] and other key clinical trial readouts are summarized in Tables 2 and 3. In the erdafitinib phase 2 trial, patients with pre-defined FGFR gene alterations were enrolled after at least one prior course of chemotherapy. Treatment-related adverse events grade 3 or higher occurred in 46% of patients and included hyponatremia, stomatitis, asthenia, and more rarely, hyperphosphatemia, as a frequent but low-grade adverse event that allows titration of erdafitinib dose.[13] The EV phase 2 trial enrolled patients previously treated with both platinum

Table 1. New first-line treatments for advanced urothelial carcinoma in the cisplatin-ineligible setting

Drug name	Study design	Overall survival	Median PFS	Objective response rate	Median time to response	Median duration of response
Pembrolizumab KEYNOTE-052	Single-arm, multicenter phase 2 study[7]	67% at 6 months	30% at 6 months	24%	2.0 months	Not reached (median followup 5 months)
Atezolizumab IMvigor 210 Cohort 1	Single-arm, multicenter phase 2 study[8]	Median: 15.9 months	2.7 months	23%	2.1 months	Not reached (median followup 17.2 months)

PFS: progression-free survival.

Table 2. New Health Canada-approved second-line treatments for metastatic urothelial carcinoma

Drug name	Study design	Median overall survival	Median PFS	Objective response rate	Median time to response	Median duration of response
Pembrolizumab	Randomized, open-label, international phase 3 study[9]	10.3 months	2.1 months	21.1%	2.1 months	Not reached (median followup 14.1 months)
Atezolizumab	Randomized, open-label, multicenter phase 3 study[11]	39.2% at 12 months	2.1 months	13.4%	Not reported	21.7 months
Avelumab	Open label, single-arm, multicenter dose-escalation phase 1 trial[10]	6.5 months	1.4 months	17%	11.4 weeks	Not reached (median followup 9.9 months)
Durvalumab	Open-label, single-arm phase 1/2 study[12]	18.2 months	1.5 months	17.8%	1.4 months	Not reached (median followup 5.8 months)
Erdafitinib	Two-arm*, multicenter, open-label phase 2 study[13]	13.8 months	5.5 months	40%	1.4 months	5.6 months

*Each arm used a different dosing and administration schedule. PFS: progression-free survival.

chemotherapy and immunotherapy. Treatment-related adverse events grade 3 or higher occurred in 54% of patients and included fatigue, rash, and peripheral sensory neuropathy.[14]

Algorithm for management of advanced urothelial carcinoma

The management algorithm is shown in Fig. 1. The algorithm begins at the point of transurethral resection of a bladder tumor (TURBT) to encompass the optimal timing of biomarker testing, which commonly uses radical cystectomy specimens or occasionally archival TURBT specimens or bladder biopsies. The primary focus of the algorithm was to support treatment and decision-making in the locally advanced or metastatic urothelial carcinoma setting (hereafter referred to as advanced urothelial carcinoma).

Management of muscle-invasive urothelial carcinoma

Diagnosis and management of urothelial carcinoma starts with TURBT (Fig. 1). Traditionally, radical cystectomy has been the cornerstone of early management of muscle-invasive disease;[25] however, some patients may receive bladder-sparing management, consisting of trimodality therapy (TMT): TURBT, chemotherapy for radiation sensitization, and external beam radiotherapy.[26] Neoadjuvant chemotherapy should be offered to eligible patients before radical cystectomy, and should be considered before TMT.[27] Patients who have residual or recurrent muscle-invasive bladder cancer (MIBC) after TMT should undergo cystectomy if they are fit for the procedure.[27]

PD-L1 reflex testing

The working group recommends that reflex testing for PD-L1 expression should be performed in patients with adverse pathological features at cystectomy, as these patients are most likely to recur and require downstream systemic therapies. This test can be done easily in the context of the existing pathology workflow, without significantly increasing the cost or complexity. Adverse features that would trigger reflex testing include one or more of the following: pathological stage T2 after prior neoadjuvant chemotherapy, pathological stage T3 or T4, lymph node involvement, lymphovascular invasion, and positive surgical margins. It is, therefore, important to provide information on prior systemic treatment to the pathologist to assist in decision-making regarding reflex testing. Cystectomy specimens are preferred for reflex testing due to the amount of tissue, quality of sample, and the representativeness of the sample, over TURBT specimens. There are limited data on the value of re-testing PD-L1 expression from a new biopsy at the time of progression; as such, re-testing is not recommended at this time.[28-30] Additional aspects of PD-L1 testing, such as assay harmonization, are discussed in more detail below.

First-line treatment of metastatic urothelial carcinoma

For patients whose disease recurs or progresses, or who present with de novo metastatic urothelial carcinoma, first-line treatment is determined by cisplatin eligibility and PD-L1

Table 3. Emerging third-line treatments under evaluation for advanced urothelial carcinoma

Drug name	Study design	Patient population	Median overall survival	Median PFS	Objective response rate	Median time to response	Median duration of response
Enfortumab vedotin EV-201	Single-arm, open-label, multicohort, phase 2 multicenter study[14]	Patients with locally advanced or metastatic urothelial cancer who previously received a CPI and previously received platinum-containing chemotherapy	11.7 months	5.8 months	44%	1.8 months	7.6 months

CPI: checkpoint inhibitor; PFS: progression-free survival.

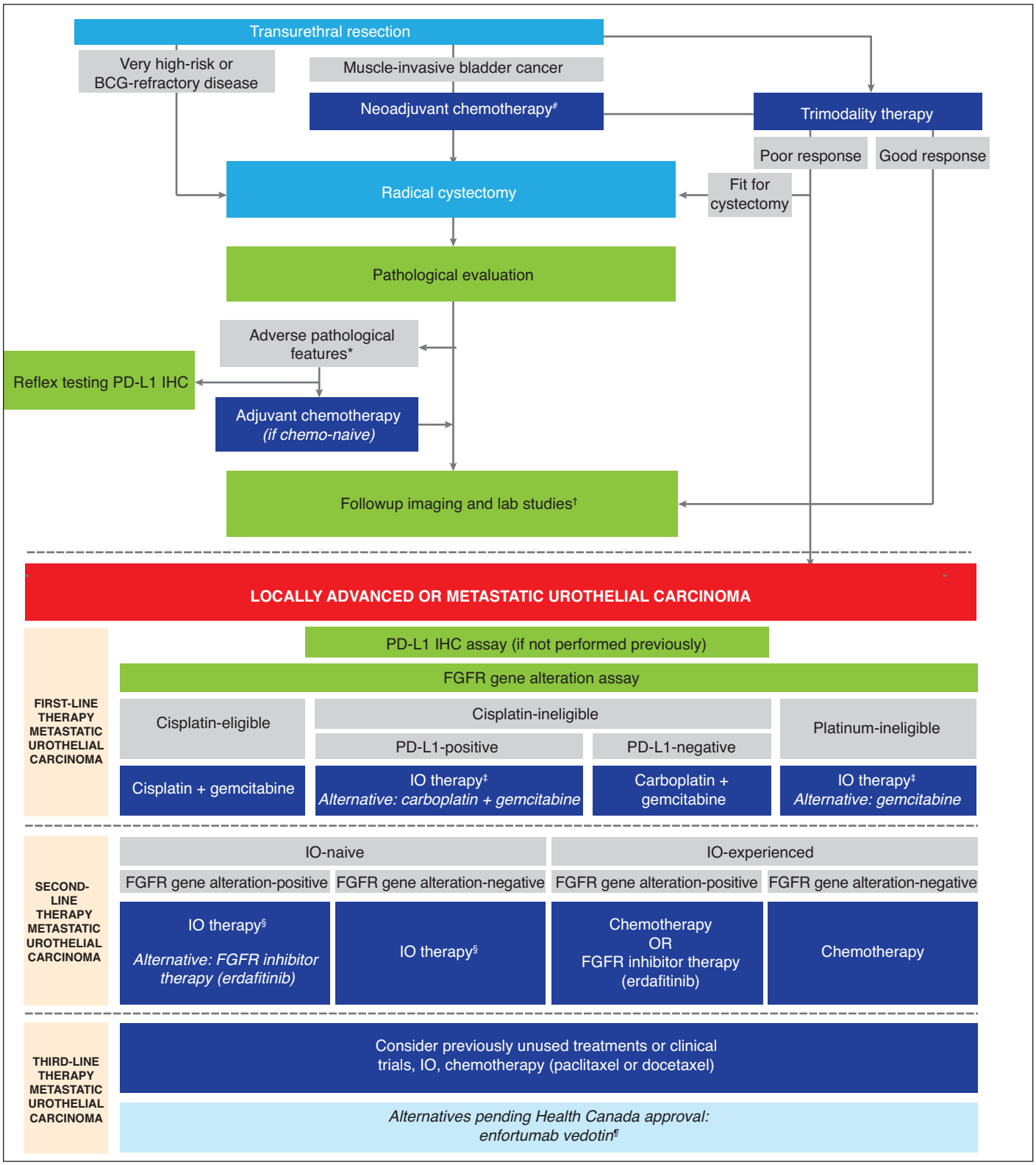

Fig. 1. Algorithm for management of advanced urothelial carcinoma. #If patients are fit for cisplatin-based neoadjuvant chemotherapy. *Adverse pathological features include lymph node metastases, lymphovascular invasion, positive surgical margins, pathological T3/T4, consider for patients T2. †Followup imaging and lab studies at 3, 6, 12, 18, 24, 36, 48, and 60 months. Imaging modalities, frequency is dependent upon pathological stage. Followup after 5 years without recurrence depends on shared decision making between the specialist and patient.[19] ‡Approved for 1L. §Approved for 2L. ¶Enfortumab vedotin anticipated approval is for post-chemo/post IO therapy. BCG: bacillus Calmette-Guerin; FGFR: fibroblast growth factor receptor; IHC: immunohistochemistry; IO: immuno-oncology; MIBC: muscle-invasive bladder cancer; PD-L1: programmed death ligand 1; TUR: transurethral resection.

expression levels (Fig. 1). The recommended initial regimen in patients who are eligible for cisplatin treatment is cisplatin and gemcitabine. Cisplatin eligibility criteria were evaluated by Galsky et al and are continuing to evolve.[31] Patients with recurrence less than 12 months from prior perioperative chemotherapy treatment usually proceed straight to second-line treatment options. Individuals with predominantly locally advanced disease who had a good response to first-line systemic therapy may benefit from consolidation with radiotherapy or surgery. The working group recommends that patients who are cisplatin-ineligible but carboplatin-eligible may receive either gemcitabine plus carboplatin doublet therapy or approved immune-oncology therapy (IO), provided testing results show high PD-L1 expression, as defined in the clinical trial for each therapy.[7,8] Patients who are ineligible for platinum chemotherapy may receive immunotherapy regardless of PD-L1 expression level.

FGFR gene alteration testing

The working group identified the initiation of first-line therapy as a clinical trigger point to test for FGFR gene alterations. The group discussed that they viewed this similarly to reflex testing, except in this case, physicians would use a clinical point as the trigger for testing rather than a specific test result as a trigger. Waiting to test for FGFR alterations until later in disease, such as once a patient has disease progression on first-line therapy and contemplating second-line options, was felt likely to cause delay of subsequent second-line treatment. Once a patient is initiating first-line therapy, it is understood that most patients will progress to second-line therapy. Rationale for this timing of the FGFR gene alteration testing is discussed in more detail below.

Second-line treatment and beyond

With chemotherapy as the standard of care for treatment of first-line advanced urothelial carcinoma, phase 3 evidence supports sequencing on disease progression from chemotherapy to immunotherapy (Fig. 1).[32] Four anti-PD-L1/PD-1 therapies (pembrolizumab, atezolizumab, avelumab, and durvalumab) are currently approved by Health Canada for this setting. Treatment with erdafitinib also represents an option for patients with FGFR gene alterations who have progressed on first- or second-line therapy. In the near future, EV may also represent an option for patients who have progressed on prior chemotherapy and immunotherapy. Taxane chemotherapy may also be used as salvage chemotherapy.[5] The working group supported having multiple treatment options accessible for second-line therapy that would allow clinicians to discuss available options with their patients and individualize therapy.

Considerations for individualizing treatment

A number of factors are often considered when selecting a second-line treatment to individualize therapy for the patient. These may include level of evidence, clinical trial characteristics of the treatment options, disease volume/characteristics, contraindications, toxicity profiles, route of administration, time to response, and regional funding criteria (Table 4). Prior therapies received by the patient will also play a role in choosing a second-line therapy. Physicians should understand their regional funding criteria in order to optimize their available treatment options. Patient preferences may also influence the choice of treatment, although patient education is important to ensure that patients are making informed choices and have reasonable expectations regarding side effects, response rate, and time to response.

Table 4. Considerations for individualizing second- and third-line treatment selection in advanced urothelial carcinoma

Therapy	Common grade 3 or greater treatment-related adverse events	Administration	Biomarker testing requirements
Immunotherapy (pembrolizumab, atezolizumab, avelumab or durvalumab)	Pneumonitis Diarrhea Fatigue Anemia Hypertension Urinary tract infection Asthenia Increased AST, ALT and/or GGT	Intravenous infusion every 2 or 3 weeks	No testing required
Erdafitinib[13]	Hyponatremia Stomatitis Asthenia	Daily oral dosing. Dose adjustments were made based on serum phosphate levels at day 14	Tumour specimen must have a confirmed FGFR gene alteration
Enfortumab vedotin[14]	Neutropenia Anemia Fatigue	Intravenous infusion on days 1, 8, and 15 of every 28-day cycle	No testing required

ALT: alanine aminotransferase; AST: aspartate transaminase; FGFR: fibroblast growth factor receptor; GGT: gamma-glutamyl transferase.

Immunotherapy

In the second-line setting, immunotherapy is indicated in patients who have received prior platinum therapy based on phase 3 data. This higher level of evidence should influence the selection of pembrolizumab over erdafitinib. The working group felt that it is rare to have absolute contraindications to immunotherapy and these drugs are generally well-tolerated. However, a minority of patients may experience major toxicities that require intervention, and treatment of patients with history of autoimmune disease should be done carefully and selectively. A minority of patients develop significant immune-related adverse events that require monitoring. A significant proportion of patients do not respond to immunotherapy; however, in patients who do respond, many achieve durable responses. Immunotherapy usually requires intravenous administration every 2–3 weeks until disease progression or unmanageable toxicity.

Erdafitinib

In the second-line setting, erdafitinib has been approved in platinum-pretreated patients based on phase 2 data. The working group discussed that erdafitinib as an oral agent might be appealing to patients as an alternative to intravenous therapy and could be an important option for patients who live in remote areas or where travelling to the hospital is an issue. Initiation of erdafitinib will require a baseline opthalmologic visit and dose titration according to serum phosphate levels. Hyperphosphatemia is a known side effect of FGFR inhibitors and occurred in 77% of patients. Ocular events are also an expected side effect with this class of therapies, and occurred in 21% of patients, with most events being grade 2 or lower, and resolving with dose interruption or reduction. Nail and skin events occurred in 49% and 52% of patients, respectively, with most events being grade 2 or lower; 13% of patients discontinued treatment because of treatment-related adverse events.[13]

It remains controversial whether patients with FGFR gene alterations are less likely to respond to immunotherapy. FGFR3 alterations are common in luminal papillary tumors, which are characterized by an immune-excluded or immune-desert phenotype that would suggest that these tumors may be less likely respond to checkpoint blockade. This is corroborated by early data from second-line trials with atezolizumab (IMvigor210) and nivolumab (Checkmate 275), but further investigation is needed.[8,33] On the other hand, Wang et al recently reported that the presence of FGFR alterations did not correlate to outcome in either IMvigor210 or Keynote045 (pembrolizumab).[34] In the phase 2 clinical trial of erdafitinib, 22 patients had received prior immunotherapy and the confirmed response rate to erdafitinib among those patients was 59%, while the prior response to immunotherapy in those patients was 5%.[13] Similar findings of responses to an FGFR inhibitor in patients who had not previously responded to immunotherapy were seen in an early report from a phase 1 trial of rogaratinib.[35] However, in both trials patients were selected due to progression on prior therapy, and these trials do not reveal the likelihood of a patient with FGFR3 alteration responding to immunotherapy.

Enfortumab vedotin (EV)

In the third-line setting, EV has been approved in the U.S. in the post-platinum, post-immunotherapy setting based on phase 2 data, and is expected to be approved for the same indication in Canada. Physicians will, therefore, have to decide between erdafintib or EV in this setting, although ideally, it would be possible to treat with both sequentially. EV is given by intravenous administration on days 1, 8, and 15 of every 28-day cycle. As Nectin-4 was detected in all patients tested in the phase 2 trial, biomarker testing is not needed for treatment with EV. Peripheral neuropathy is a known toxicity with this type of agent and occurred in 50% of patients. Most occurrences were grade 2 or less, and most had resolved or had grade 1 peripheral neuropathy at last followup. Rash was an anticipated on-target toxicity and occurred in 48% of patients, with 75% being grade 2 or less. Treatment-related hyperglycemia occurred in 11% of patients, regardless of known hyperglycemia at baseline. Treatment-related adverse events led to discontinuation in 12% of patients.[14]

Considerations regarding biomarker testing for advanced bladder cancer

PD-L1 immunohistochemistry testing

In addition to reflex testing of PD-L1 in high-risk cystectomy patients, in some cases the physician will need to order a PD-L1 test if testing did not occur as a reflex test, such as high-risk TMT patients and de-novo metastatic patients.

Different in vitro diagnostic assays (IVDs) have been developed as companion diagnostics for different anti-PD-L1 therapies, and laboratories may also choose to use a laboratory-developed test. For the purpose of testing PD-L1 status in urothelial carcinoma, any validated test can be used as long as the assay provides results that are concordant with the approved companion diagnostic tested in clinical trials;[7,10-12,36] that is, the assay should provide the same classification of patients by PD-L1 expression levels as in those trials. Harmonization between laboratories and standardization of how PD-L1 testing results are reported in urothelial carcinoma will be required.

FGFR gene alteration testing

Testing for FGFR gene alterations prior to initiating first-line treatment for advanced urothelial carcinoma will need to be requisitioned by the treating physician. Because prior neoadjuvant therapy may influence diagnostic interpretation and the assessment of risk variables, the requisition should state what prior therapy the patient has had, what other testing has been done, and to whom/where the report should be sent; the latter is important to avoid delays. However, unlike for the PD-L1 IHC assay, the working group recommended against having the FGFR gene alteration testing performed on a reflex basis for patients with adverse pathological features in the cystectomy specimen because, in contrast to immunotherapy, erdafitinib will only be used in the second-line, and there is adequate time to test it if ordered at the time of initiating first-line therapy. In addition, limited data suggest that FGFR gene alterations are stable over time.[37] Later testing will be associated with significant cost savings, especially with the higher cost of this type of testing compared to IHC testing for PD-L1 expression. Of all patients receiving first-line treatment, approximately 46% will go on to receive second-line treatment.[38] A two-week turn-around time between specimen reception at the test center and report signing out was defined as the standard benchmark adequate for FGFR gene-alteration testing.

FGFR gene-alteration testing will likely be done by next-generation sequencing (NGS), due to the ability to test multiple genes and mutation types simultaneously on NGS. The test will make use of archived cystectomy specimens if available, and otherwise TUR or biopsy specimens. When sending tissue for FGFR gene-alteration testing, a representative formalin-fixed paraffin-embedded (FFPE) block is preferred, but unstained slides may also be accepted. Pathologists from the holding lab should request the specimen requirements from the testing lab the samples will be sent to. The working group recommended that in cystectomy specimens, the pathologist should designate a block that should be maintained in the pathology lab for all future molecular testing in order to ensure that the tissue is not exhausted for research or other endeavors. In addition, the pathologist can mark the slides that are optimal for molecular testing. The importance of sending tissue quickly when the test is requisitioned should be stressed to the referring lab. FGFR gene-alteration testing performed on circulating tumor DNA (ctDNA) from plasma samples has potential clinical utility, however, due its relatively low sensitivity, it should be reserved for cases in which diagnostic tissue is not available.[39,40]

Limitations of this work

Rapid advances in this therapeutic area will likely lead to the approval of new therapies and potentially new biomarkers, and the algorithm described herein will need to be revisited at regular intervals to incorporate these advances. The timing of biomarker testing as delineated in the algorithm is based on expert opinion only, which may be the cause for some debate. Some of the recommended therapies lack high-level evidence because they are supported only by single-arm trials. We anticipate that the level of evidence supporting the newer therapies and their sequencing in the algorithm will continue to evolve.

Future directions in metastatic urothelial carcinoma

Results of several ongoing phase 2 and phase 3 trials are anticipated over the next few years and these trials will provide additional results to guide the treatment of metastatic urothelial carcinoma. Phase 3 trials of immunotherapy compared to chemotherapy in the first-line setting are ongoing (NCT02853305, NCT02807636), as well as phase 3 trials of erdafitinib (NCT03390504) and EV (NCT03474107). Combination therapies are being investigated, in addition to new agents, such as novel FGFR inhibitors and immunotherapies. In addition, research into predictive biomarkers is ongoing. Deficiencies in DNA damage repair genes, tumor mutational burden, and microsatellite instability

Summary of key points

Treatment of advanced urothelial carcinoma

- First-line therapy
  - Gemcitabine + cisplatin remains the standard treatment (phase 3 evidence)
  - Gemcitabine + carboplatin can be used in patients deemed unfit for cisplatin
  - Patients ineligible for cisplatin now also have the option of using immunotherapy according to Health Canada criteria (non-randomized phase 2 evidence)
- Second-line and third-line therapy
  - Immunotherapy is recommended for patients who progressed on prior chemotherapy (phase 3 evidence)
  - Taxane-based chemotherapy may be used
  - Anti-FGFR therapy may be considered as an alternative in patients with FGFR alterations who progressed on prior chemotherapy or immunotherapy (phase 2 evidence)
  - Pending Health Canada approval, enfortumab vedotin may be considered in patients who have progressed on prior chemotherapy and immunotherapy (phase 2 evidence)
- Optimal sequencing of treatment in second-line is not known at this time based on the current data. Clinical judgement should be used to determine the best course of action for an individual patient

Biomarker testing for advanced urothelial carcinoma

- PD-L1 expression levels should be performed as a reflex test in patients with adverse pathological features at cystectomy in order to have results available when the patient needs first-line treatment if progression occurs.
- FGFR gene alteration testing should be requisitioned/triggered by a patient's initiation of first-line therapy for advanced urothelial carcinoma in order to have results available when the patient needs second-line treatment

are examples of biomarkers under investigation to predict response to immune checkpoint inhibitors, and targetable genetic alterations, such as EGFR, ERBB2, ERBB3, PIK3CA, and RAS have been found as likely oncogenic drivers of subsets of bladder cancers.[41] New therapeutic options and the potential for additional biomarkers to guide patient selection are likely to reshape the treatment landscape for advanced bladder cancer in the near future.

Competing interests: Dr. Black has been an advisory board member or equivalent for Abbvie, Asieris, AstraZeneca, Astellas, Bayer, Biosyent, BMS, EMD-Serono, Fergene, Ferring, H3-Biomedicine, Janssen, Merck, Roche, Sanofi, and Urogen; a speakers' bureau member for Abbvie, Biosyent, Ferring, Janssen, Pfizer, and TerSera; has received grants/honoraria from a Bayer, GSK, iProgen, and Sanofi; has participated in clinical trials supported by Astellas, AstraZeneca, BMS, Genentech, Janssen, MDx Health, Pacific Edge, Sitka, and Therelase; and shares a patent with Decipher Biosciences. Dr. Alimohamed has been an advisory board member for Astellas, AstraZeneca, Janssen, Merck, and Pfizer. Dr. Berman has received honoraria and/or travel expenses from Bayer and Janssen. Dr. Blais has been an ad hoc consultant for AstraZeneca, Bayer, BI, BMS, Merck, Novartis, Roche, Pfizer, Sanofi, and Servier. Dr. Eigl has received honoraria and travel support from Astellas, AstraZeneca, Bayer, Janssen, Merck, and Roche. Dr. Kassouf has received grants/honoraria from Amgen, Astellas, and Janssen. Dr. Ong has received payment (including gifts or in-kind compensation) from Astellas, AstraZeneca, Bayer, BMS, EMD Serono, Janssen, and Merck; and has received grants from Astellas and Astra Zeneca. Dr. Sridhar has attended advisory boards for Astellas; received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated in clinical trials supported by Agenisys, Imclone, OGX, Roche, and Sanofi Aventis. Dr. Stockley has been an advisory board member for AstraZeneca; received honoraria from Amgen, Astellas, AstraZeneca, BMS, and Janssen; and received a research grant from AstraZeneca. Dr. van der Kwast has received honoraria from Janssen. Mr. Hew and Ms. Park-Wyllie are employees of Janssen Canada. Dr. North has attended advisory boards for Astellas; has received grants/honoraria from Astellas, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Janssen, and Sanofi. The remaining authors report no competing personal or financial interests related to this work.

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