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Genitourinary Cancers (S Gupta, Section Editor)

Treatment Approaches for Cisplatin-Ineligible Patients with Invasive Bladder Cancer

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Opinion statement

Cisplatin has been established as an important agent in the neoadjuvant setting prior to radical cystectomy (RC) surgery for muscle-invasive urothelial cancer (MIUC) as well as in the unresectable or metastatic urothelial carcinoma (mUC) setting. Unfortunately, many patients in practice are felt to be "cisplatin-ineligible." Thus, it is vital that we develop treatment approaches and novel therapeutics for this population. We evaluate therapeutic alternatives to cisplatin-based treatment. For patients undergoing RC, there is no recommended alternative to neoadjuvant cisplatin-based combination therapy, and upfront RC or clinical trials are preferable. For patients receiving "bladder-sparing" radiation, concurrent radiosensitizing chemotherapies may be used, and several trials are also underway. For cisplatin-ineligible patients with mUC who are eligible for chemotherapy, carboplatin-based or split-dose cisplatin-based regimens may be employed. Pembrolizumab and atezolizumab offer options as first-line therapy for cisplatin-ineligible patients with high PD-L1 expression. The results of trials combining checkpoint inhibitors or platinum-based chemotherapy plus PD1/PD-L1 inhibitors are eagerly awaited. For platinum or chemotherapy-ineligible patients with mUC, immune checkpoint inhibitors such as inhibitors of programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) are approved regardless of PD-L1 expression. However, given limited effectiveness of first-line PD-1/PD-L1 inhibitor monotherapy in tumors with low PD-L1 expression, trials in this space are critical.

Introduction

With an estimated 430,000 new cases in 2012, bladder cancer is the ninth most common cancer in the world [1]. During the same year, bladder cancer was estimated to cause 165,000 deaths. The primary risk factor worldwide is tobacco smoking, conferring about a 2.5 times elevated risk compared to lifelong non-smokers [2] and accounting for half of bladder cancer cases [3–5] and 40% of bladder cancer deaths [4]. Given the delay between exposure to tobacco smoke and development of the disease, current bladder cancer trends often reflect prevalence of smoking from several decades prior. Thus, while bladder cancer incidence and mortality are decreasing in developed Western nations, industrializing nations are not expected to see any decreases in bladder cancer for several decades [1].

When bladder cancer is detected early, it may be treated with transurethral resection and sometimes intravesical therapies for high-risk non-muscle invasive disease. However, for muscle-invasive urothelial carcinoma (MIUC), standard approaches include radical cystectomy (RC) or nephroureterectomy in conjunction with neoadjuvant cisplatin-based chemotherapy, which is supported by randomized phase III trials. In those who are ineligible for or refuse radical surgery, "bladder-sparing" trimodality therapy consisting of aggressive transurethral resection followed by concurrent radiation and chemotherapy is offered. For unresectable or metastatic disease, systemic chemotherapy is a standard first-line approach. Cisplatin forms the backbone of neoadjuvant chemotherapy, radiosensitizing chemotherapy, and first-line palliative regimens, and it appears to be superior to carboplatin-based regimens for metastatic urothelial carcinoma (mUC) [6], although no randomized comparisons have been made. Unfortunately, patients with bladder cancer have comorbidities as a result of age or smoking history that limits the use of cisplatin. Among patients presenting with stage IV bladder cancer in the SEER-Medicare database, approximately half received no chemotherapy, and only 20.5% received cisplatin [7]. Another retrospective analysis of patients with advanced bladder cancer found that half of patients received cisplatin-based treatment and that cisplatin use was an independent favorable prognostic factor, independent of baseline characteristics or comorbidities [8]. In fact, based on available data, approximately one quarter of patients who did not receive cisplatin may have been cisplatin-eligible; conversely, a proportion of patients who were cisplatin-ineligible by consensus criteria appeared to be receiving cisplatin. Physician concern about age was a primary factor in limiting the use of cisplatin. Thus, "standard" cisplatin-based chemotherapy may actually not be used for many patients with bladder cancer.

In this article, we examine the criteria used to determine eligibility for cisplatin-based treatment and present novel approaches to treating patients ultimately deemed cisplatin-ineligible. This has major implications for practice since a substantial proportion of patients seen in real-world practice may have comorbidities limiting the use of cisplatin.

Who is cisplatin-ineligible?

1. Consensus definitions

In 1997, the European Organization for Research and Treatment of Cancer (EORTC) conducted a survey of genitourinary oncologists to try to define cisplatin ineligibility [9]. The majority of respondents considered preserved renal function, defined as creatinine clearance (CrCl) ≥ 60 mL/min, and World Health Organization (WHO) performance status (PS) 0 or 1 as requirements for cisplatin treatment.

In 2011, Galsky and colleagues conducted a review of criteria used to determine eligibility for cisplatin in clinical trials [10, 11]. First, they identified age as a criterion used in some trials to exclude patients from cisplatin but determined that there was little evidence for the use of this criterion alone to

determine cisplatin eligibility [12]. Second, the authors retained a standard definition of adequate renal function for cisplatin of CrCl ≥ 60 mL/min but noted that the use of different equations for estimating renal function might impact this assessment. Third, the role of solitary kidney (especially relevant to patients with upper-tract urothelial carcinoma requiring nephroureterectomy) in determining cisplatin eligibility was unclear. Fourth, poor performance status was felt to be a predictor of increased toxicity and decreased efficacy [13, 14]. Finally, other comorbidities were considered, including congestive heart failure, neuropathy, and hearing loss. After considering these potential criteria, Galsky and colleagues conducted a survey of genitourinary oncologists and used the results to propose a working group definition of cisplatin ineligibility consisting of the following: the WHO or Eastern Cooperative Oncology Group (ECOG) PS of ≥ 2, CrCl < 60 mL/min, Common Terminology Criteria for Adverse Events (CTCAE) version 4 grade ≥ 2 audiometric hearing loss or peripheral neuropathy, or New York Heart Association (NYHA) class III heart failure.

2. Renal impairment

One series demonstrated that 30–50% of patients undergoing RC had estimated CrCl or glomerular filtration rate (GFR) below the cutoff of 60 mL/min or mL/min/1.73 m^2, respectively, commonly used to determine sufficient renal function for cisplatin [15]. However, as noted above, renal function is often estimated indirectly using serum creatinine and other clinical factors, since direct measurement requires cumbersome urine collections. The use of different equations for estimating renal function may result in a different assessment of "cisplatin eligibility."

The International Society for Geriatric Oncology Task Force on Renal Safety in the Elderly suggested that the Modification of Diet in Renal Disease (MDRD) equation for estimating GFR may be preferred over the Cockroft-Gault equation in patients with chronic kidney disease [16]. Galsky and colleagues noted in their report that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation may perform even better than the MDRD equation and warranted further study in cancer patients [11]. Indeed, a follow-up retrospective analysis demonstrated that the CKD-EPI formula was less likely than the Cockroft-Gault formula to deem patients ineligible for cisplatin-based therapy; however, the implications for clinical decision-making were unclear [17].

Since the risk of cisplatin-induced nephrotoxicity is unlikely to be dichotomous, a risk prediction model may help refine assessment of suitable renal function. A model including age, cisplatin dose, hypertension, and serum albumin was predictive of acute kidney injury after cisplatin [18]. In this model, baseline renal function was actually not significantly associated with cisplatin-induced kidney injury, but this study excluded patients with creatinine > 1.5.

In the setting of neoadjuvant chemotherapy, cisplatin may be feasible in patients with estimated GFR < 60 mL/min/1.73 m^2. Compared with patients without renal impairment, 30 patients with low GFRs completed a similar number of cycles with similar toxicity and no difference in renal function or ability to complete cystectomy, but with more dose delays and reductions [19]. The authors acknowledged the risk of selection bias given that these patients with impaired renal function may have had unique characteristics that led clinicians to feel comfortable to use cisplatin, which may limit generalizability

to all patients with renal impairment. In addition, this study defined GFR based on the lesser of the estimated GFRs calculated by the Cockcroft-Gault versus MDRD formulas and therefore may have underestimated true renal function in the "low GFR" group, leading to bias toward the null. This study calls into question the complete exclusion of patients from cisplatin based on GFR, but prospective studies will be required in order to identify a population of patients with renal impairment for whom cisplatin is safe.

Some clinicians have made use of a "split-dose" regimen for borderline cases with calculated creatinine clearance 40–60 mL/min, wherein cisplatin is separated across 2 treatment days. There have been no obvious differences in tolerability or outcomes between standard and spit-dose regimens [20–24], although no randomized comparisons have been performed.

Chemotherapy strategies

If a patient has been deemed cisplatin ineligible with the caveats noted above but is still otherwise felt to be a candidate for cytotoxic chemotherapy, several alternative strategies have been used. For patients undergoing cystectomy, a retrospective analysis of patients receiving neoadjuvant cisplatin-based chemotherapy versus a combination of gemcitabine and carboplatin demonstrated no difference in rates of pathologic complete response (pCR), approximately 30% in both groups, and no significant difference in disease-specific survival [25]. Additionally, other retrospective studies suggest a more modest pCR rate of ~20–25% with gemcitabine plus carboplatin [26, 27]. One randomized phase III trial attempted to evaluated adjuvant gemcitabine alone for cisplatin-ineligible MIUC, but could not complete accrual and had significant imbalance in randomization of node-positive patients [28]. In sum, there is no strong prospective or randomized evidence to support non-cisplatin-based neoadjuvant therapy, and the National Comprehensive Cancer Network guidelines do not recommend perioperative non-cisplatin-based chemotherapy [29]. Instead, such patients should be considered for clinical trials of perioperative systemic therapy, described below. For upper-tract urothelial carcinoma, the recent phase III POUT study offers some evidence for adjuvant platinum-based therapy: this study tested adjuvant gemcitabine plus either cisplatin or carboplatin in high-risk resected upper-tract urothelial carcinomas versus treatment at recurrence, and the adjuvant strategy resulted in significant prolongation in disease-free survival [30]. However, the confidence interval for the disease-free survival hazard ratio for carboplatin-treated patients was wide due to small number and overlapped 1, and further follow-up will be needed to assess the relative effects of carboplatin versus cisplatin as well as the effect on overall survival.

Frequently, patients may be ineligible for both cisplatin and cystectomy, or may decline cystectomy. "Bladder-sparing" regimens using maximal transurethral resection, definitive radiation, and chemotherapy may be used instead. Multiple trials have investigated the role of concurrent radiosensitizing chemotherapy. One trial enrolled patients with high-risk T1 and T2+ bladder cancer and randomized them to radiation alone or with

the addition of 5-fluorouricil and platinum [31]. Patients with CrCl < 60 were treated with carboplatin instead of cisplatin. Overall, a complete clinical response was seen in 72% of patients, which decreased to only 64% at 10-year follow-up. Those receiving cisplatin did appear to have a higher rate of complete response and higher overall survival compared with the group treated with carboplatin. A similar trial randomized patients to radiation with or without 5-fluorouricil and mitomycin-C [32]. This was modeled on the regimen used for anal cancer and eliminated the need for platinum, although one third of patients did receive neoadjuvant cisplatin-based treatment. This trial included patients with PS as low as 2 and CrCl as low as 25 mL/min. The addition of chemotherapy significantly improved locoregional disease-free survival but not overall survival. Single-agent gemcitabine has also been used, albeit in a trial of patients with normal renal function [33], and may provide a less toxic treatment option, although no direct comparisons of efficacy or toxicity have been made between these various radiosensitizing regimens.

Several studies have attempted to substitute carboplatin for cisplatin for treatment of advanced bladder cancer. Single-agent carboplatin appeared to have a low response rate [34], so subsequent studies used combination regimens. A regimen of dose-dense doxorubicin, gemcitabine, carboplatin, and paclitaxel was tested in patients with impaired renal function and resulted in overall response rate of 56% with 28% complete responses at 45-month follow-up, but was complicated by significant myelosuppression [35]. Substituting carboplatin for cisplatin in a regimen of methotrexate, vinblastine, epirucibin, and cisplatin (M-VEC) resulted in significantly lower response rate although improved toxicity [36]. Similarly, the substitution of carboplatin for cisplatin in the methotrexate, carboplatin, and vinblastine (M-CAVI) regimen reduced efficacy in cisplatin-eligible patients with mUC [37], and M-CAVI was no more effective than gemcitabine and carboplatin in cisplatin-ineligible patients with mUC and carried higher toxicity [38]. Gemcitabine and carboplatin were inferior to gemcitabine and cisplatin in cisplatin-eligible patients with mUC [39], and carboplatin and paclitaxel were inferior to standard methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) [40] in cisplatin-eligible patients with mUC [41]. A pooled meta-analysis of randomized controlled trials concluded that there was a higher rate of complete response and overall response with cisplatin-based treatment in mUC compared to carboplatin-based, with unclear impact on survival endpoints [42]. Finally, oxaliplatin plus gemcitabine has been evaluated in small studies with demonstrated modest activity [43, 44]. However, despite the relative lack of nephrotoxicity, the neurotoxicity can be problematic with oxaliplatin.

Non-platinum-containing regimens have also been evaluated for mUC. Interestingly, a systematic review and meta-analysis of standard gemcitabine and carboplatin versus gemcitabine plus taxanes demonstrated median response rates, progression-free survival, and overall survival that were very similar between the two strategies across 27 included studies [45]. As expected, there were differences in toxicity, with more myelosuppression associated with carboplatin and more neuropathy associated with taxanes.

Immune checkpoint inhibitor strategies

Immune checkpoint inhibitors have changed the landscape of treatment options available to bladder cancer patients, especially those ineligible for cisplatin. There are now five inhibitors of the programmed death-1/programmed death-ligand 1 pathway approved by the Food and Drug Administration for treatment of advanced bladder cancer.

Atezolizumab, a PD-L1 inhibitor, was studied in the single-arm phase 2 IMvigor 210 trial as first-line therapy for locally advanced or metastatic bladder cancer. Cohort 1 specifically enrolled patients who were ineligible for cisplatin. In an updated analysis, overall response rate was 23%, with 9% complete responses and 19 of 27 responses ongoing [46]. Median duration-of-response had not been reached. Higher tumor mutation burden was associated with increased response rates, but response rates were similar regardless of PD-L1 status.

Cisplatin-ineligible patients were also targeted in the KEYNOTE-052 study of first-line pembrolizumab, a PD-1 inhibitor. Half of these patients had CrCl 30–60 mL/min, one third had a PS of 2, and 9% had both renal impairment and PS of 2. Overall response rate was 24%, and 83% of responses were ongoing as of data cutoff [47]. Response rates were enriched in groups with higher PD-L1 expression, and most responses were seen in the group with highest PD-L1 expression.

The KEYNOTE-045 randomized patients after progression on first-line platinum-based therapy to pembrolizumab or standard-of-care second-line chemotherapy, and it demonstrated both increased median overall survival with pembrolizumab [48••] as well as prolonged time-to-deterioration in health-related quality-of-life compared with chemotherapy [49]. Response rates were similar between PD-L1-high and PD-L1-low groups, and the survival benefit was retained in both groups.

Nivolumab was also studied in the second-line setting after progression on platinum-based therapy in the phase 2 single-arm Checkmate 275 trial. Overall response rate was 19.6%, with higher PD-L1 expression correlated with higher response but not limited to PD-L1-expressing tumors [50•].

The phase 1 JAVELIN trial of avelumab, a PD-L1 inhibitor, demonstrated complete or partial responses in 17% of patients [51•]. Although the trial included 13 cisplatin-ineligible patients, half of whom had received other prior platinum; only patients treated with prior platinum were included in efficacy analyses.

Finally, a phase 1/2 study of the PD-L1 inhibitor durvalumab in patients who had almost all received prior platinum demonstrated overall response rate of 17.8%, including 7 complete responses [52•]. Responses were again more frequent but not limited to PD-L1-expressing tumors.

The phase 3 KEYNOTE-361 and IMvigor130 studies are testing PD-1/PD-L1 blockade (with pembrolizumab and atezolizumab, respectively) with chemotherapy compared to these agents alone, without chemotherapy, or to chemotherapy alone [53, 54]. The data safety monitoring committee observed that patients with PD-L1-low status had decreased overall survival when treated with PD-1/PD-L1 blockade alone, compared with chemotherapy. Therefore, both

trials stopped enrollment of patients with PD-L1-low tumors to the single-agent PD-1/PD-L1 blockade arms, and the FDA issued a warning against frontline use of single-agent PD-1/PD-L1 inhibitors. However, the clinical implications of this were limited, since historic response rates to first-line platinum-based chemotherapy regimens were much higher than those seen with PD-1/PD-L1 inhibitors, regardless of PD-L1 status. Thus, the standard-of-care first-line treatment remained platinum-based therapy for those eligible, and single-agent PD-1/PD-L1 inhibitors are still used only for platinum-ineligible (not just cisplatin-ineligible) patients and after failure of prior platinum-based regimens.

Phase III trials of adjuvant therapy are evaluating various PD1 and PD-L1 inhibitors for cisplatin-ineligible patients in addition to cisplatin-refusing patients (if they did not receive neoadjuvant cisplatin-based chemotherapy). Recently, non-randomized phase II trials revealed the feasibility and promising activity of neoadjuvant atezolizumab or pembrolizumab given as single agents for cisplatin-ineligible or cisplatin-refusing patients. In particular, neoadjuvant pembrolizumab monotherapy resulted in a 42% of patients with pCR at the time of RC [55•], in comparison with historical pCR rates of around 15% with no neoadjuvant treatment. PD-L1 expression and tumor mutation burden both seemed to predict for pCR, and over half of patients with a combined positive PD-L1 score of ≥ 10% achieved pCR. Similarly, neoadjuvant atezolizumab monotherapy resulted in a pCR rate of 29% overall and 40% in patients with PD-L1-expressing tumors [56]. Indeed, phase III trials are being planned to evaluate a PD-1 inhibitor monotherapy approach as neoadjuvant therapy for cisplatin-ineligible patients with MIUC. Preliminarily, the combination of cisplatin-based chemotherapy and pembrolizumab also demonstrated promising pCR rates in a phase Ib/II study [57], suggesting that this strategy may be applicable to cisplatin-ineligible patients by using a non-cisplatin backbone. Indeed, this study is also accruing patients to a cisplatin-ineligible cohort combining gemcitabine with pembrolizumab; similarly, the backbone of gemcitabine plus carboplatin may warrant evaluation in combination with PD-1/PD-L1 inhibitors.

Future directions

Eight years ago, one of us (G.S.) argued that the common practice of separating out cisplatin-eligible from cisplatin-ineligible patients was impeding advances for bladder cancer and limiting the generalizability of results from trials limited to cisplatin-eligible patients [58]. Furthermore, shifting trial development toward chemotherapy-ineligible and cisplatin-ineligible patients could bridge the chasm between "efficacy" and "effectiveness" by making trial results more applicable to real-world patients [7].

Since that time, the era of immunotherapy has dramatically changed the landscape of treatments available to cisplatin-ineligible patients. Yet, as the FDA warning indicates, platinum-based chemotherapy is still a staple of bladder cancer therapy and has not been replaced by immune checkpoint inhibitors. Much of the ongoing clinical trial work still focuses on immune checkpoint inhibitors and expanding their indications to other settings (Table 1). For example, PD-1/PD-L1 inhibitors will be assessed in BCG-refractory non-muscle invasive bladder cancer (NCT02625961 and NCT02844816), in the

Table 1. Ongoing trials including cisplatin-ineligible patients with urothelial carcinoma

Disease setting	Phase	NCT number	Study name	Study drugs
Neoadjuvant	II	NCT02662309		Atezo
	II	NCT03674424	AURA	Avel ± ddMAVC or gem/cis (cis-eligible) or ± gem/paclitaxel (cis-ineligible)
	I/II	NCT03498196	A Window of Opportunity	Avel
	II	NCT03534492	NEODURVARIB	Durva + olaparib
	II	Pending		Durva ± oleclumab
	II	NCT02845323		Nivo ± urelumab
	Ib	NCT03532451	PrE0807	Nivo ± lirilumab
	II	NCT02736266		Pembro
	Ib/II	NCT02365766	HCRN GU14–188	Pembro + gem/cis (cis-eligible) or gem (cis-ineligible)
Adjuvant	III	NCT02450331	IMvigor010	Atezo vs. surveillance
	III	NCT02632409	CheckMate 274	Nivo vs. placebo
	III	NCT03244384	AMBASSADOR	Pembro vs. surveillance
Bladder-sparing chemo/RT	II	NCT0320435		Atezo
	II	Pending		Avel
Post-chemo/RT maintenance	II	NCT03697850	BladderSpar	Atezo
mUC, 1st line	III	NCT02807636	IMvigor130	Atezo ± gem/platinum vs. gem/platinum
	II	NCT03628716		Atezo + CV301 vaccine (cis-ineligible or post-cisplatin)
	III	NCT03682068	NILE	Durva ± treme + gem/platinum vs. gem/platinum
	III	NCT02516241	DANUBE	Durva ± treme vs. gem/platinum
	II	NCT0349846	BAYOU	Durva ± olaparib
	III	NCT03036098	CheckMate 901	Ipi/nivo vs. gem/platinum (vs. nivo/gem/cis)
	III	NCT02853305	KEYNOTE-361	Pembro ± gem/platinum vs. gem/platinum
	II	NCT03534804	PemCab	Pembro + cabozantinib
mUC, maintenance post-chemo	III	NCT02603432	JAVELIN Bladder 100	Avel vs. surveillance
	II	NCT02500121		Pembro vs. surveillance
mUC, post-chemo or cis-ineligible	IIIb	NCT03084471	STRONG	Durva ± treme (non-randomized)
	II	NCT03472560	JAVELIN Medley VEGF	Avel + axitinib
	Ib	NCT02546661	BISCAY	AZD4547, durva, olaparib, AZD1775, vistusertib, AZD9150, selumetinib (based on genomics)
mUC, any line	I	NCT02826564		SBRT + pembro (sequential vs. concurrent)

atezo, atezolizumab; *avel*, avelumab; *cis*, cisplatin; *durva*, durvalumab; *gem*, gemcitabine; *ipi*, ipilimumab; *nivo*, nivolumab; *SBRT*, stereotactic body radiotherapy; *pembro*, pembrolizumab; *treme*, tremelimumab

neoadjuvant (NCT02736266 and NCT02662309) and adjuvant (NCT02450331 and NCT03244384) settings, and as maintenance after first-line platinum therapy (NCT02500121 and NCT02603432).

A second question is whether chemotherapy and immunotherapy should be used in combination, either in the neoadjuvant setting (NCT02365766 and NCT03674424) or in advanced disease (NCT02853305, NCT02807636, NCT03036098, and NCT03682068).

Third, will blockade of multiple immune checkpoints be superior to chemotherapy alone or chemotherapy with PD-1/PD-L1 blockade? CheckMate 901 (NCT03036098) and DANUBE (NCT02516241) are phase 3 trials involving the combination of PD-1/PD-L1 plus CTLA-4 inhibitors, versus chemotherapy with or without PD-1/PD-L1 inhibitors. NCT03084471 will compare this combination strategy after failure of prior chemotherapy. Cisplatin-ineligible patients are eligible for enrollment in all of these trials, although CheckMate 901 randomizes them only to the combination of nivolumab plus ipilimumab versus standard-of-care chemotherapy, with the combination of cisplatin-based chemotherapy plus nivolumab being evaluated only in cisplatin-eligible patients. Furthermore, the NILE trial evaluates chemotherapy alone or in combination with durvalumab ± tremelimumab for both cisplatin-eligible and cisplatin-ineligible patients. Finally, additional immune-stimulatory strategies are being tested, including vaccines such as CV301 in combination with atezolizumab (NCT03628716).

Fourth, can we increase response rates to immunotherapy through the addition of targeted agents or radiation? In the neoadjuvant setting, several trials are open or pending. NCT02845323 is a phase 2 study of neoadjuvant nivolumab with or without urelumab, an antibody that activates $CD137^{+}$ immune cells, enhancing cytotoxic T cell response against tumor cells. NCT03532451 is a phase 1 study of neoadjuvant nivolumab plus lirilumab, an inhibitor of the KIR signaling that may enhance natural killer cell activity; cohort 2 is for cisplatin-ineligible MIBC. A pending trial of neoadjuvant durvalumab with or without oleclumab, an inhibitor of adenosine deaminase, will specifically target cisplatin-ineligible MIBC. For cystectomy-ineligible patients, atezolizumab is being tested together with "bladder-sparing" radiation, both as monotherapy and (in a forthcoming Southwestern Oncology Group trial) in combination with 5-fluorocil and platinum. In the advanced setting, the phase 2 BAYOU study (NCT0349846) will evaluate durvalumab with or without the PARP inhibitor olaparib. Another phase 2 study will evaluate pembrolizumab plus cabozantinib for cisplatin-ineligible patients (NCT03534804) since vascular endothelial growth factor-targeting agents may have additional effects on immune suppressive cells.

Conclusion

Bladder cancer tends to affect older adults with comorbidities and may also lead to local complications that result in renal impairment. Thus, the use of cisplatin-based therapy may be challenging or contraindicated. However, multiple trials have demonstrated that cisplatin-based therapy remains the standard-of-care both in the perioperative setting for localized disease and for advanced disease. Cisplatin-ineligible patients are not currently recommended

to receive any perioperative chemotherapy, while carboplatin or taxanes may be substituted in the advanced setting. The definition of "cisplatin-ineligible" remains unclear, especially in regard to renal impairment. Estimation of renal function by different methods may lead to different results, and the Cockroft-Gault equation used frequently in clinical practice and for trial eligibility may underestimate renal function and result in unnecessary exclusion of patients from cisplatin-based therapy. Newer equations and risk models may help refine the use of cisplatin in patients with borderline renal function. Meanwhile, the advent of immune checkpoint inhibitors has opened new therapeutic possibilities to patients ineligible for cisplatin or for chemotherapy more broadly, although with the caveat that platinum-based therapy is still preferable as the first-line standard therapy in the advanced setting. Clinical trials increasingly include cisplatin-ineligible patients, and their results will therefore be more generalizable.

Compliance with Ethical Standards

Conflict of Interest

David J. Einstein has received research funding (paid to Beth Israel Deaconess Medical Center, Boston, MA) for clinical trials from Bristol-Myers Squibb and TrovaGene.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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