Perioperative Therapy for Muscle Invasive Bladder Cancer

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KEYWORDS

- Urinary bladder neoplasms • Neoadjuvant therapy • Adjuvant therapy
- Chemotherapy • Radiotherapy • Radical cystectomy • Chemotherapy

KEY POINTS

- Bladder cancer has a high incidence of local and distant recurrence, which may be the result of micrometastatic disease at the time of localized treatment.
- Eradicating deposits of micrometastases from bladder cancer is best achieved via perioperative systemic neoadjuvant or adjuvant therapy.
- Postcystectomy nomograms and risk stratification help to identify patients who may benefit from adjuvant therapy.
- Use of platinum-based combination chemotherapy in the neoadjuvant setting improves survival. Adjuvant chemotherapy is also beneficial, although the evidence is less robust.
- Investigation of molecular pathways underlying bladder cancer has led to the discovery of genomic alterations, which may lead to the development of patient-specific therapies.

INTRODUCTION

Urothelial carcinoma (UC) of the bladder is the fourth most commonly diagnosed malignancy in the United States. About 20% to 30% of patients present with muscle invasive ($\geq$T2) bladder cancer (MIBC).[1] Initial treatment for most of these patients consists of localized therapy, including surgery or radiation; however, the risk of recurrence after localized therapy exceeds 50%,[2] and the 5-year mortality rate ranges from 33% to

73%.[3] It is thought that the high incidence of local and distant recurrence is due to micrometastatic disease at the time of localized treatment. Therefore, perioperative systemic therapy is often used in the form of neoadjuvant or adjuvant therapy, with the goal of eradicating deposits of micrometastases.

Based on level I evidence (meta-analysis of randomized trials), the current gold standard for the treatment of MIBC is neoadjuvant cisplatin-based chemotherapy, followed by surgery, which shows an increased overall survival benefit of 5%.[4] Despite this evidence, recent studies have reported that this therapeutic strategy is still not widely used.[5]

Adjuvant treatment has increased survival in patients with different malignancies such as breast and colon cancer.[6,7] In MIBC, the role of adjuvant chemotherapy has been investigated throughout the last 3 decades, but the benefit still remains controversial. Most clinical trials evaluating the impact of adjuvant chemotherapy on MIBC have important methodological limitations, including small sample size, early termination owing to poor accrual, few events (deaths), and different chemotherapy regimens, leading to unequivocal results and few studies reporting a survival benefit.

This article discusses advantages and disadvantages of each therapeutic strategy, highlighting the most important studies supporting their use.

STRATIFICATION OF RISK AND PROGNOSTIC VARIABLES

Whereas there is strong evidence for the use of neoadjuvant chemotherapy in MIBC, there has been little information on the risk stratification of this group in the prelocalized treatment setting. In the meta-analysis of neoadjuvant trials performed in 2005, there was no specific risk stratification involving age, gender, clinical T or N stage, or performance status.[4]

The most widely used risk stratification in the precystectomy setting is staging. However, there is a large difference between clinical and pathologic staging at radical cystectomy (RC), with up to 54% of patients being upstaged[8] and 18% being downstaged at the time of surgery.[9] A nomogram designed to help predict pT3 or pT4 at RC was found to confer only a modest (4%) improvement over clinical staging alone.[10] Qureshi and colleagues[11] constructed an artificial neural network with 2 difference categories (Ta/T1 and T2–T4), using variables including genomic alterations, smoking status, gender, carcinoma in situ (CIS), metaplasia, architecture, and location of the tumor. This model predicted progression-free survival (PFS) and 1-year cancer-specific survival (CSS) at 80% and 82% accuracy, respectively. Catto and colleagues'[12] neuro–fuzzy models predicted recurrence-free survival (RFS) of Ta-T4 cases with 88% to 95% accuracy. The prediction model included p53, mismatch repair proteins, stage, grade, age, smoking status, and previous cancer. Although all of these models could be used to help identify patients who need neoadjuvant therapy, it has not proved to be better than clinical staging alone.

There have been multiple postcystectomy nomograms and risk stratifications that help identify patients who may benefit from adjuvant therapy.[13–18] Most prediction models include pathologic features from RC, including lymphovascular invasion (LVI), grade, and lymph node involvement, yet there is still only a minimal increase in accuracy of survival or recurrence compared with staging alone.

Karakiewicz and colleagues[13] created probability nomograms including age, T stage, N stage, grade, LVI, CIS, adjuvant radiotherapy, adjuvant chemotherapy, and neoadjuvant chemotherapy, which predict 2-, 5-, and 8-year RFS with 78% accuracy. Shariat and colleagues[14,15] had a similar probability nomogram, using the same categories as Karakiewicz, which predicted 2-, 5-, and 8-year overall survival (OS) and

bladder CSS at 79% and 73% accuracy, respectively. Additional nomograms created by the groups of Bassi and Bochner[16,17] have been found to be able to predict 5-year RFS and 5-year OS at 75% and 76% accuracy, respectively.

One of the best markers for survival is a complete pathologic response (pT0). There is approximately a 15% complete response (CR) from transurethral resection alone, whereas there is about a 35% to 45% CR after neoadjuvant chemotherapy.[18] In the Southwest Oncology Group (SWOG) neoadjuvant trial, 85% of patients with pT0 were alive after 5 years of follow-up.[19]

Biomarkers to help predict response to therapy could possibly increase the CR rate. A 20-gene expression profile has been shown to predict advanced or metastatic UC; however, this requires further prospective validation before incorporating it into routine clinical practice.[20] The COXEN (CO eXpression ExtapolatioN) model has shown promise in the preclinical setting at predicting which cell lines will respond to gemcitabine/cisplatin or MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) therapy. This model is currently being tested in a prospective clinical trial.[21] Recently, Van Allen and colleagues[22] found that mutations in ERCC2, a DNA damage repair protein, correlate with CR in patients receiving cisplatin-based combination neoadjuvant chemotherapy. There is a need to validate these markers and investigate additional novel prediction models in both precystectomy and postcystectomy settings.

NEOADJUVANT STRATEGIES FOR MUSCLE INVASIVE BLADDER CANCER
Advantages

Neoadjuvant chemotherapy has several advantages. The 2 main advantages are the ability to eradicate micrometastases early, and the potential to downstage chemotherapy sensitive tumors.[23] Approximately 38% of patients who are able to receive cisplatin combination chemotherapy have a pathologic CR, compared with the pathologic CR rate of 6% to 15% for patients who did not receive cisplatin-based combination neoadjuvant chemotherapy.[2,19,20] Pathologic CR has been shown to strongly predict outcomes, and is used as an important end point for patient prognosis.[23]

Disadvantages

There are some potential disadvantages to neoadjuvant chemotherapy. Because there are no validated ways to predict response to neoadjuvant chemotherapy, patients with chemoresistant bladder tumors who undergo neoadjuvant chemotherapy are inevitably delayed from receipt of a potentially curative surgical therapeutic option (ie, RC). This delay and its association with survival outcomes remain unclear. In addition, there is some concern that neoadjuvant chemotherapy may subsequently increase the risk of complications during RC, although this has recently been contended in population-based studies.[24,25]

Evidence Summary

Chemotherapy
Randomized clinical trials Multiple clinical trials have demonstrated the benefit of neoadjuvant chemotherapy (**Table 1**). The Nordic I trial included 311 patients with T1-T4NxM0 who were randomized to receive 2 cycles of cisplatin and doxorubicin versus no neoadjuvant treatment before RC. All patients received 20 Gy of irradiation before RC. There was no statistically significant difference in OS or CSS at 5 years. However, in a subgroup analysis of patients with pT3-T4 disease, a 15% survival benefit was seen in patients receiving chemotherapy.[26] In the Nordic II trial, 309 patients were randomized to receive 3 cycles of neoadjuvant cisplatin and methotrexate or to RC alone. Again, no overall significant difference in 5-year survival was seen

Table 1
Randomized trials for neoadjuvant therapy

Series	Study Population	Year	No. of Patients	Chemotherapy	Follow-up[a] (mo) (Range)	Overall Survival[b] (%)	Overall Survival HR (95% CI)	Significant (Yes/No)
Cortesi[74]	T2–T4, N0, M0	(Unpublished)	171	Cisplatin Methotrexate Epirubicin Vinblastine	—	52.4 vs 57.7	—	No
Wallace[75]	T2–T4, Nx, M0	1991	255[c]	Cisplatin	—	71.1 vs 65.8	1.13 (0.80–1.57)	No
Coppin[76]	T2–T4b	1996	102	Cisplatin	78	16 vs 13, P = .34	0.75 (90% CI 0.50–1.12)	No
Abol-Enein[77]	T2–T4a, Nx, M0	1997	196	Cisplatin Methotrexate Vinblastine	—	—	—	—
Martinez-Pineiro[78]	T2–T4a, Nx–N2, M0	1995	122	Cisplatin	78.2 (48–101)	35.5 vs 37.3	—	No
Italian Bladder Study (GISTV)[79]	T2–T4a	1996	206	Methotrexate Vinblastine Adriamycin Cisplatin	—	—	—	No
International Collaboration of Trialists[30]	T2–T4a, N0-x, M0	2011	976	Cisplatin Methotrexate Vinblastine	120	36 vs 30, P = .037	0.84 (0.72–0.99)	Yes

Study	Stage	Year	No.	Regimen	Follow-up[a]	OS	HR (CI)[b]	Benefit
Malmstrom[80] **Bassi**	T3–T4, N0 Any T, N+	1996	325	Cisplatin Doxorubicin	60	59 vs 51, P = .1	—	No
Bassi (GUONE)[81]	T2–T4b, N0-x, M0	2002	153	Cisplatin Methotrexate Vinblastine	—	52 vs 57.6	—	No
Sherif (Nordic II)[27]	T2–T4a, Nx, M0	2002	317	Cisplatin and methotrexate Cisplatin and adriamycin	56.4	56 vs 48	0.80 (0.64–0.99)	Yes
Grossman (SWOG Intergroup)[19]	T2–T4a	2003	317	Methotrexate Vinblastine Adriamycin Cisplatin	104	57 vs 43, P = .06	1.33 (1.00–1.76)	Yes

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Mean or median follow-up time (in months) as reported by each study during time of publication. Types of range reported include minimum to maximum, interquartile range, and 95% confidence intervals.

[b] Based on number of events out of total number of patients in treatment (neoadjuvant) versus control arm (local treatment: radical cystectomy or radiotherapy).

[c] All 255 patients underwent neoadjuvant chemotherapy, but the control arm received local treatment in the form of radiotherapy in 2 different regimens: (1) 159 patients received 45–50 Gy in 22 fractions and (2) 96 patients received 65 Gy in 22 fractions + 10–15 Gy.

between the treatment groups (53%, neoadjuvant plus RC vs 46%, RC only).[27] One limitation to both Nordic trials is that they both used unconventional regimens that are uncommonly used in current practice (doxorubicin/cisplatin and methotrexate/cisplatin, respectively). However, a combined analysis of the 2 Nordic trials revealed an OS favoring neoadjuvant chemotherapy (5-year survival 56% vs 48%; $P = .049$), highlighting the efficacy of cisplatin-based neoadjuvant chemotherapy.[28]

The largest neoadjuvant prospective trial, published in 1999, included 976 patients (T2-T4N0) who were randomized to receive 3 cycles with the combination chemotherapy regimen of cisplatin, methotrexate, and vinblastine (CMV) or no systemic therapy. Patients were then treated with 1 of the following local therapies: (1) radiation therapy (RT), (2) a combination of low-dose radiotherapy and RC, or (3) RC alone.[29] Although the trial did not initially demonstrate statistical significance in survival, a long-term update, presented in 2002, demonstrated a 10-year OS benefit credited to neoadjuvant chemotherapy (36% vs 30%; hazard ratio [HR] 0.84).[30] The type of localized treatment did not change the survival outcomes. Pathologic CR was attained in 32.5% of patients receiving neoadjuvant therapy, versus 12.3% with RC alone.[30]

The SWOG performed a prospective, randomized controlled trial of 317 patients with T2-T4aN0M0 UC comparing 3 cycles of neoadjuvant MVAC chemotherapy preceding RC with RC alone. Although the trial did not show a statistically significant advantage for neoadjuvant therapy with 5-year OS (57% vs 43%; $P = .06$) or median survival (77 vs 46 mo), the trial is still considered to demonstrate level I superiority of neoadjuvant therapy because the original goal of statistically significant difference, defined as a one-sided $P<.05$, was attained. Patients receiving neoadjuvant therapy had a CR rate of 38%, compared with 15% with RC alone. Most patients (81%–82%) were able to proceed to cystectomy after receiving neoadjuvant chemotherapy. Toxicities of chemotherapy were manageable, with no toxic deaths, grade 4 neutropenia seen in 33%, and grade 3 gastrointestinal toxicities seen in 17%. No increase in postoperative complications was observed.[20]

Finally, single-agent platinum did not yield significantly better outcomes. No single platinum-based combination regimen combined with any local therapy (RC alone, radiotherapy alone, or radiotherapy in combination with RC) has demonstrated superiority over only localized therapy. Cisplatin tends to be the platinum agent used in most patients (>90%), with carboplatin used only in 6% to 7% of patients, owing to carboplatin being shown to be significantly inferior to cisplatin-based treatment.[31]

Nonrandomized prospective and retrospective studies The 2 main neoadjuvant chemotherapy regimens, gemcitabine-cisplatin (GC) and MVAC, have only been compared in retrospective studies. Current data suggest similar rates of pathologic CR and survival outcomes with both regimens (relative risk of CR 0.97, 95% confidence interval [CI] 0.60–1.56; $P = .9$).[32]

Dose-dense MVAC is being used more frequently in the neoadjuvant setting. A phase II study explored the efficacy and safety of this regimen with pegfilgrastim support in patients with muscle-invasive UC. Neoadjuvant chemotherapy resulted in significant pathologic and radiologic downstaging (49% achieved CR defined as ≤ pT1N0M0) with a favorable toxicity profile.[33] One advantage of this strategy is the short time to complete the 4 cycles of therapy, thus not delaying surgical treatment in patients who are not sensitive to systemic chemotherapy. Dose-dense therapy is being increasingly investigated by centers of excellence, particularly for bladder UC, and may also be a promising alternative to GC for high-grade upper tract urothelial carcinoma (UTUC).[34]

Meta-analysis The pooling of data from the aforementioned randomized clinical trials using meta-analysis statistical techniques has allowed us to advance our understanding regarding the true utility of neoadjuvant chemotherapy in bladder cancer, in addition to statistically increasing the total number of patients in both arms. The latest published meta-analysis of 11 randomized trials was performed by the Advanced Bladder Cancer Meta-Analysis Collaboration, and included 3005 patients. There was a significant survival benefit (HR 0.86, 95% CI 0.77–0.95; $P = .003$) among those who received neoadjuvant cisplatin-based chemotherapy, compared with those who did not; this translated into a 5% absolute increase in 5-year OS and a 9% absolute increase in 5-year disease-free survival (DFS) in comparison with RC alone.[4] Given this demonstrated survival benefit, in 2012 the National Comprehensive Cancer Network Guidelines recommend the use of neoadjuvant platinum-based combination chemotherapy for cT2 and strongly recommend it for cT3 node-negative disease,[35] similar to guidelines from the European Association of Urology[36] and European Society of Medical Oncology.[37]

At present, there is no effective regimen for patients with poor performance status and/or renal inefficiencies. There has been a meta-analysis comparing carboplatin-based with cisplatin-based chemotherapy regimens, with cisplatin-based therapies showing clear superiority (relative risk 3.54; $P = .005$).[31]

Radiation therapy

UC is relatively radiosensitive, and in the neoadjuvant setting RT may be able to prevent intraoperative seeding of tumor cells in the operative field and to sterilize microscopic extension in the perivesical tissues. There exists only one randomized trial demonstrating the superiority of preoperative radiotherapy over cystectomy alone in 2-year OS in patients with T3 bladder cancer.[38,39] Studies performed in the 1980s investigated the role of preoperative radiotherapy in either T2 or all stages of bladder cancer, and no marked benefits were found. One of the more recent studies was a phase III trial in the United States, which had a total of 140 patients who were randomized to receive 2000 Gy of pelvic irradiation followed by RC within 1 week, or RC alone. The 5-year survival rates were 43% (95% CI 30%–56%) and 53% (95% CI 41%–65%), respectively ($P = .23$).[40] Since then, research into this treatment modality has stagnated. In the contemporary management of bladder cancer, the role of RT in the neoadjuvant setting seems limited. With recent advances in the use of more targeted radiotherapies such as intensity-modulated RT, which has been shown in some studies to significantly reduce the volume of normal tissues affected while treating a variety of abdominopelvic tumors, neoadjuvant radiotherapy may resurface as a potential investigative option for patients with bladder cancer.[41,42]

ADJUVANT STRATEGIES FOR MUSCLE INVASIVE BLADDER CANCER
Advantages

The major advantage of administering adjuvant treatment is the appropriate patient selection according to the risk of recurrence. The adequate pathologic staging reduces the risk of overtreatment and allows for the selection of patients most likely to benefit from systemic therapy.[43] A large retrospective cohort evaluated discrepancies in clinical and pathologic staging in patients who underwent RC for MIBC. Clinical understaging was identified in approximately 50% of the patients, and pathologic downstaging occurred in 18%.[9]

Adjuvant chemotherapy does not delay local treatment for patients with chemoresistant tumors. Moreover, when neoadjuvant was compared with adjuvant chemotherapy, there were no differences in perioperative morbidity.[44] Therefore, adjuvant therapy certainly has its place in contemporary management.

Disadvantages

The major disadvantage to adjuvant treatment is delaying the treatment of micrometastatic disease. In addition, response to treatment measured by pathologic downstaging may provide important prognostic information.[45] With adjuvant chemotherapy, the only way to assess the benefit of this treatment is the absence of disease progression during long-term follow-up.

Another potential disadvantage is the possibility of postsurgical complications that may preclude patients from receiving adjuvant cisplatin-based chemotherapy. Donat and colleagues[46] have found at their high-volume tertiary center that nearly one-third (30%) of patients develop complications after RC of Clavien grade 2 or higher. Although surgical morbidity at their center may reflect the more complicated case mix they encounter, this highlights the importance of considering contributors to postoperative morbidity, as this may delay the administration of adjuvant chemotherapy.

Summary of Evidence

Chemotherapy

Randomized clinical trials Several randomized clinical trials attempted to define the role of adjuvant treatment in MIBC (**Table 2**). In 1994, Studer and colleagues[47] reported the results of a study designed to evaluate the role of adjuvant cisplatin monotherapy after RC. Seventy-seven patients with nonmetastatic MIBC were stratified based on nodal status (stage pN0 vs pN1–N2) and were randomly assigned to observation or adjuvant chemotherapy. In this study, no differences in OS were observed between the 2 groups in patients with all disease stages. Similarly, patients who had pN1-N2 did not benefit from the adjuvant treatment.[47]

Skinner and colleagues[48] randomized 91 patients with T3/T4 or positive lymph node MIBC to receive adjuvant cisplatin, doxorubicin, and cyclophosphamide or to observation after RC. In this study, median OS was 4.3 years for patients who received chemotherapy versus 2.4 years in the observation group ($P = .0062$). Of note, these results could be explained by several methodological biases.[48]

A German phase III clinical trial showed a benefit in OS and PFS with adjuvant chemotherapy (MVAC or MVEC [methotrexate, vinblastine, epirubicin, cisplatin]). This study was prematurely closed because of suggested striking benefits of adjuvant chemotherapy, so only a small number of patients was included in the final analysis. Of note, patients assigned to the observation arm did not receive any further treatment at the time of recurrence. By contrast, another German study showed that patients treated with adjuvant MVEC versus observation did not show significant differences in OS.[49]

Another clinical trial compared 2 neoadjuvant cycles followed by 3 adjuvant cycles after RC versus 5 adjuvant cycles of MVAC. This study enrolled 140 patients and suggested that neoadjuvant chemotherapy may be more feasible than adjuvant chemotherapy, although no difference in survival outcome was demonstrated.[44]

Recently, trials using cisplatin/gemcitabine-based regimens in the adjuvant setting were performed, based on results of this regimen in the metastatic setting. The prospective Italian trial of 194 patients was underpowered to demonstrate a survival difference in patients receiving 4 cycles of adjuvant GC (HR 1.29).[50] The Spanish Oncology Genitourinary Group trial randomized 340 patients with high-risk disease (T3–T4 or lymph node positive) to receive 4 cycles of paclitaxel, gemcitabine, and cisplatin (PCG) versus observation. Adjuvant PCG resulted in a significant increase in OS compared with no chemotherapy (60% vs 31%, HR 0.44).[51] Of note, both trials were prematurely closed, and the power of these analyses limits the conclusion regarding the efficacy of this strategy.

A biomarker-driven clinical trial, based on altered p53 levels, randomized patients with organ-confined disease (pT1 or pT2, N0M0) to 3 cycles of MVAC versus observation. No statistically significant difference in clinical outcome was identified based on p53 status.[52]

Most recently, the results of the European Organization for Research and Treatment of Cancer (EORTC) intergroup randomized phase III clinical trial was presented. The study's initial plan was to enroll a total of 1344 patients with MIBC to receive 4 cycles of adjuvant chemotherapy according to physician choice (GC, MVAC, or dose-dense MVAC) versus 6 cycles of deferred therapy at the time of recurrence. The trial was prematurely closed after enrollment of 284 patients with pT3-T4 and/or lymph node–positive and M0 disease. Adjuvant chemotherapy resulted in a statistically significant difference in PFS: 46.8% in the adjuvant treatment arm versus 29.5% in patients in the deferred arm. However, the median OS (primary end point) was 53.6% for patients who received immediate treatment versus 47.7% for patients in the deferred chemotherapy group (HR 0.78, 95% CI 0.56–1.10; P = .13).[53]

Nonrandomized prospective and retrospective studies Logothesis and colleagues[54] are among the first to report the impact of adjuvant chemotherapy in patients with MIBC. In this study, 71 patients presenting with pT3b, pT4, N1, or vascular/lymphatic invasion were treated with cisplatin, cyclophosphamide, and adriamycin. The 5-year survival rate for patients treated with this strategy was 70%, compared with 37% for those patients who were part of a historical control treated with surgery alone. Similar results in terms of long-term survival were reported from another study in which adjuvant CMV (n = 23) was compared with the same drugs plus doxorubicin (n = 12).[55] These studies supported the rationale for randomized investigation of this therapeutic strategy.

A large retrospective study evaluated 932 patients from 11 centers who received adjuvant chemotherapy after RC, and found that adjuvant chemotherapy was independently associated with longer OS (HR 0.83, 95% CI 0.72–0.97; P = .017). As expected, the benefit was higher in patients who presented both pT3 stage and lymph node–positive disease (HR 0.75, 95% CI 0.62–0.90; P = .002).[56]

Meta-analysis As the results from the prospective randomized clinical trials were not definitive and have several methodological limitations, meta-analyses have been conducted to help interpret the available data. The Advanced Bladder Cancer Meta-Analysis Collaboration conducted a meta-analysis with individual patient data from 491 patients enrolled in 6 studies. In this analysis, patients who were treated with adjuvant chemotherapy had a relative reduction in the risk of death of 25%.[57]

Recently, a study-level meta-analysis of 9 randomized trials including 945 patients was published.[58] In this updated analysis, patients receiving adjuvant treatment with cisplatin-based regimens had a DFS benefit (HR 0.66, 95% CI 0.45–0.91, P = .014) and OS benefit (HR 0.78, 95% CI 0.61–0.99; P = .044) compared with those who underwent RC alone. Moreover, lymph node–positive patients seem to have greater benefit with this strategy. Interpretation of these results should be taken cautiously, as individual patient data were not analyzed.[59–61] Therefore, the next study to look out for will be an updated individual patient data meta-analysis including the latest EORTC intergroup study, as the pooled HR is likely to demonstrate OS benefit for adjuvant chemotherapy. Such findings may influence clinical practice substantially.

Radiation therapy

RT has no well-established role in the adjuvant setting. Although the rationale of decreasing local recurrences may lead to subsequently lower rates of distant disease,

Table 2
Randomized trials for adjuvant therapy

Series	Year	Study Population	No. of Patients Total	Treatment Arm (Chemotherapy Regimen)	Control Arm (Locoregional Treatment)	Follow-Up (mo) (Range)[a]	Overall Survival (%)	Overall Survival HR (95% CI)	Significance (Yes/No)
Freiha[82]	1996	T3–T4, Any N	55	Cisplatin and methotrexate Vinblastine	Radical cystectomy	62 (24–96)	63 vs 36	0.74 (0.36–1.53)	No
Otto[83]	2001	T3/N1–N22	108	Methotrexate Vinblastine Epirubicin Cisplatin	Radical cystectomy	44	50.9 vs 54.7	0.82 (0.48–1.38)	No
Skinner[48]	1991	T3–T4, N0 Any T, N+	102	Patients 1–17: 16 cisplatin-based, in combinations with doxorubicin, cyclophosphamide, 5-fluorouracil, vinblastine, or bleomycin Patients 18–91: Cisplatin, doxorubicin, cyclophosphamide	Radical cystectomy	—	51.6 vs 28.8	0.75 (0.48–1.19)	Yes

Lehmann[84]	2006	Any T, N+ T3–T4, Any N	49	MVAC or MVEC (1 patient received carboplatin instead of cisplatin)	Radical cystectomy	120	17.4 vs 26.9	1.75 (0.95–3.23)	No
Studer[47]	1994	Any T, Any N	91	Cisplatin	Radical cystectomy	69 (36–96)	57 vs 54	1.02 (0.57–1.84)	No
Stadler[52]	2011	T1–T2, N0 p53+	114	Methotrexate Vinblastine Doxorubicin Cisplatin	Radical cystectomy	64.8 (61.2–70.8)	20.7 vs 16.1	1.11 (0.45–2.72)	No
Italian trial[50]	2012	T2 (grade 3) T3–T4, N0–N2	194	Gemcitabine Cisplatin	Radical cystectomy	35 (15–57)	46.6 vs 39.9	1.29 (0.84–1.99)	No
Spanish trial[51]	2010	T3–T4, N0 Any T, N+	142	Paclitaxel Gemcitabine Cisplatin	Radical cystectomy	29.8 (1–95)	60 vs 31	0.38 (0.22–0.65)	Yes
EORTC Intergroup Trial[53]	2014	T3–T4, N0 Any T, N+	284	Gemcitabine, cisplatin or MVAC or High-dose MVAC	Radical cystectomy	83.6 (–) vs 86.5 (–)	53.6 vs 47.7	0.78 (0.56–1.08)	No

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; MVEC, methotrexate, vinblastine, epirubicin, cisplatin.

^a Mean or median follow-up time (in months) as reported by each study during time of publication. Types of range reported include minimum to maximum, interquartile range, and 95% confidence intervals.

the use of RT after an RC has resulted in suboptimal results and has been associated with higher toxicity levels.

A small randomized trial showed that adjuvant radiotherapy may improve both local control and DFS in comparison with surgery alone.[62] In addition, a retrospective study reported similar results.[63] Results of a phase III randomized clinical trial were reported in 2006 at the American Society of Clinical Oncology Annual Meeting, whereby no statistical differences were observed in DFS rates in high-risk patients with bladder cancer who received adjuvant chemoradiation with cisplatin plus gemcitabine versus radiation alone.[64]

Regarding the limitations of these studies, further evaluation and a better characterization of patients who may benefit from this therapy are warranted. Similarly to the neoadjuvant setting, modern RT techniques may have a role in improving the toxicity profile and adding clinical benefit.

MOLECULAR BIOLOGY AND TARGETED THERAPIES

Our understanding of the molecular pathways underlying bladder cancer has benefited from recent advances in technologies such as high-throughput transcript profiling, microarrays, metabolomics, and proteomics. Intense research efforts in this area have borne fruit through the discovery of numerous molecular markers. These markers may be useful for screening, early diagnosis, and surveillance in addition to staging and prognosis.[65] Leading the effort is The Cancer Genome Atlas project (TCGA), which has identified potential therapeutic targets in 69% of UC tumors, including pathways suitable for further investigation.[66] It has been estimated that at least 60% of genomic alterations could be treated by drugs that are already available or under clinical testing.[67] Some potential new targets for treatment intervention have been described for UC, including the most recurrent reported mutations in the receptor tyrosine kinases (*RTK*)-*RAS-RAF*, phosphoinositide 3-kinase (*PI3K*)/*AKT*/mammalian target of rapamycin pathways (mTOR), and regulators of G1-S cell cycle progression such as TP53 and RB1.[67]

Other potential therapeutic targets lie in the mutation and/or gene amplifications present in a large proportion of urothelial tumors, including *FGFR3* mutations,[68] *PTEN* deletions, and *FGFR1*, *CCND1*, and *MDM2* amplifications.[66] More than half of UC have also been found to contain aberrations of the chromatin remodeling genes (*UTX*, *MLL-MLL3*, *CREBBP-EP300*, *NCOR1*, *ARID1A*, and *CHD6*) and, more recently, *STAG2* mutations.[67,69] Nevertheless, it must be cautioned that the functional effect of mutations in these genes encoding epigenomic regulatory proteins remains relatively unknown. It may be possible that identifying these driving genomic alterations, even if occurring in only a small subset of patients with bladder cancer, may lead to the development of patient-specific therapies. For example, recently described mutations in *TSC1* were useful in helping investigators examine the response to mTOR inhibitors such as everolimus, or in the *PIK3CA* gene, mutated in up to 26% of cases, which may predict sensitivity to *PIK3CA*/mTOR inhibitors.[70–73] Cancer immunotherapy also represents an exciting avenue for research, with the Food and Drug Administration recently granting "Breakthrough Therapy Designation" for MPDL3280A (anti-PDL1) in bladder cancer.

ONGOING CLINICAL TRIALS

Several clinical investigations have also been performed to address some open questions in the neoadjuvant and adjuvant treatment scenarios. A phase III trial clinical trial of GC versus high-dose intensity MVAC, with regimen selection decisions driven by

genomic profile, will help to define the optimal chemotherapy regimen in the perioperative setting for patients with locally advanced UC (NCT01812369). In addition, the role of taxanes in the neoadjuvant setting is being evaluated in a phase I study consisting of administering 4 cycles of cabazitaxel and cisplatin before RC. The study's primary end point is response rate (NCT01616875). In the adjuvant setting, a German phase III study was designed to evaluate gemcitabine alone versus nontreatment in the control arm in a subset of patients who are not suitable for cisplatin-based chemotherapy (NCT00146276). This study, like the previous studies in the adjuvant setting, was closed because of poor accrual, but can still be valuable. Another study is evaluating the impact of an immunotherapeutic agent recMAGE-A3 + AS-15 in patients with MIBC who were surgically treated and are positive for the antigen MAGE-A3 (MAGNOLIA) (NCT01435356). Finally, a randomized phase II study is evaluating DN24-02 (a Her2 targeting autologous antigen-presenting cell-based vaccine) as adjuvant therapy in subjects with high-risk HER2+ UC.

SUMMARY AND FUTURE DIRECTIONS

MIBC is an aggressive disease associated with poor survival rates. Although RC alone may result in cure for a subset of patients, the higher rates of relapse suggest that early administration of systemic therapy may improve clinical outcomes. Therefore, contemporary management of patients with MIBC involves the combination of surgery, systemic chemotherapy, and chemoradiation in select patients who are candidates for bladder preservation.

Neoadjuvant treatment with cisplatin-based combination regimens is an established standard of care and has improved long-term survival in MIBC. However, owing to the low rates of adoption of neoadjuvant chemotherapy, clinicians will still face the decision of whether to administer adjuvant chemotherapy to high-risk patients who have not received neoadjuvant chemotherapy. In the absence of definitive evidence justifying the recommendation of adjuvant chemotherapy, administering systemic therapy after an RC in high-risk patients is still an option if clinical trials are not available.

In the genomic era, the biology underlying MIBC has been elucidated. The TCGA has characterized genes and molecular pathways involved in cancer development and tumor progression, providing insights to improve the therapeutic arsenal. In addition, these results may add to the development of biomarkers to select patients for the available or new therapies. Of importance is that immunotherapy strategies have produced encouraging results in patients with advanced disease. However, how this new knowledge will affect the perioperative treatment in MIBC is still undefined, and efforts should be undertaken to integrate molecular aspects in innovative clinical trial designs in this setting.

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