Neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer: The likelihood of initiation and completion

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ABSTRACT

Introduction: Chemotherapy was shown to improve survival in patients undergoing radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC). The initiation and completion rates for perioperative chemotherapy are variable. Our aim is to compare the likelihood of initiating and completing neoadjuvant (NAC) and adjuvant chemotherapy (AC) in patients who underwent RC for MIBC.

Materials and Methods: We performed a retrospective analysis of patients who underwent RC between 1992 and 2011. NAC was advised for patients with clinical stage ≥T2, hydronephrosis, extensive lymphovascular invasion (LVI), or prostatic stromal invasion. Patients with ≥pT3 or lymph node metastases were considered for AC.

Results: A total of 363 patients were considered for perioperative chemotherapy. Among the 141 patients who were offered NAC, 125 (88.6%) initiated NAC. A total of 222 were considered for AC, and 151 (68.0%) initiated AC (P < 0.001). In the NAC group, 118 (83.5%) completed planned number of cycles of chemotherapy and 7 (5.6%) did not complete the planned chemotherapy. In the AC group, 79 (35.5%) completed at least four cycles and 72 (47.3%) could not complete the planned cycles (P < 0.001).

Conclusions: Patients with MIBC are more likely to initiate and complete NAC than AC.

Key words: Adjuvant, bladder cancer, chemotherapy, completion, neoadjuvant, radical cystectomy

INTRODUCTION

Bladder cancer (BC) is the fourth most common cancer in the US. The annual incidence is estimated to be 73,510.¹ Although most patients have non-invasive bladder tumors, 20-40% either present with or later develop muscle invasion.²,³ Radical cystectomy (RC) is the standard surgical treatment for clinically localized muscle-invasive bladder cancer (MIBC).³,⁴ However, nearly 50% of patients with MIBC develop metastases and die of BC. Such a high failure rate is explained by the presence of occult metastatic BC at diagnosis.⁵,⁶ Hence, the role of systemic chemotherapy emerged.

Urothelial BC has shown sensitivity to Cisplatin-based combination chemotherapy. Objective response rates in the order of 50% have been attained with combination chemotherapy.⁷ There are several factors to consider while offering perioperative chemotherapy to a patient undergoing RC. The advantages and disadvantages of neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) are discussed in Table 1.

After a decision is made to administer chemotherapy, to achieve maximum benefit the planned regimen should be initiated and the planned number of cycles must be completed at an optimal dosage. However, due to various reasons chemotherapy is often not initiated or it is initiated but not completed. The aim of our study is to evaluate and compare the likelihood of initiating and completing neoadjuvant and adjuvant chemotherapy in patients with MIBC.
MATERIALS AND METHODS

Upon obtaining an institutional review board approval, we performed a retrospective analysis of patients who underwent RC and urinary diversion (UD) by a single surgical team between 1992 and 2011. Patients who were candidates for chemotherapy were identified and included in the analysis. Data on whether NAC or AC was recommended, initiated, discontinued, or completed was obtained and analyzed.

Prior to 2004, NAC was recommended for patients with clinical stage T3 or higher stage, hydronephrosis, extensive lymphovascular invasion (LVI), or prostatic stromal invasion. Since 2004, patients with clinical T2 BC were also being offered NAC. Patients with pathological T3b or T4 or lymph node metastases were considered for AC. The typical chemotherapy regimens were gemcitabine plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). On occasions, carboplatin was substituted for cisplatin at the discretion of the oncologist. At any given instance, the chemotherapy regimen was similar for NAC and AC. Both AC and NAC were not recommended to patients who were unlikely to tolerate chemotherapy due to renal impairment or other debilitating morbidities.

The Chi-square/Fisher exact test was used to compare categorical variables. \( P \leq 0.05 \) was considered significant.

RESULTS

A total of 363 patients underwent RC and UD and were considered for perioperative chemotherapy—141 for NAC and 222 for AC. The mean age was 66 years in NAC group and 67.5 years in AC group (\( P = 0.13 \)). Of these patients, 79% were men and 21% were women. The male to female ratio was 4:1 in both groups. Completion of chemotherapy was defined as receiving the planned number of cycles predetermined by the medical oncologist.

Among the 141 patients offered NAC, 125 (88.6%) initiated NAC. Further, 98 patients (78.4%) completed at least 3 cycles, 20 (16%) completed 2 cycles as planned, and 7 (5.6%) did not complete the planned number of cycles. From the 222 patients recommended to receive AC, 151 (68.0%) initiated the treatment. Of patients who initiated AC, 79 (52.7%) completed at least 4 cycles and 72 (47.3%) could not complete the planned four cycles. Overall, only 79 (35.5%) of patients who are candidates for AC received the prescribed number of cycles, while 118 (83.5%) of NAC candidates received the planned number of cycles. Patients who were offered NAC were more likely to initiate (\( P < 0.001 \)) and complete (\( P < 0.001 \)) chemotherapy [Figure 1]. The reason for not initiating NAC was patient preference, while for AC the reasons were either patient preference or presence of medical condition or surgical complication interfering with chemotherapy initiation. The reasons for discontinuing NAC or AC were patient preference, chemotherapy intolerability, or development of complications [Table 2].

DISCUSSION

Most patients receive perioperative chemotherapy for MIBC in the adjuvant setting.\(^8,9\) There are several difficulties in administering chemotherapy in the adjuvant setting. The typical patient undergoing RC is in his/her sixth or seventh
decade of life and has significant associated comorbidities. Moreover, RC and UD are associated with complications in approximately 30% of patients.

In a study by Donat et al., 83% of patients who experienced complications following RC and UD had significant complications (grade 2-5, modified Clavien system), which prevented or delayed the use of adjuvant chemotherapy. The psychological impact of a major surgery may further impede adjuvant therapy, and thus fewer patients receive AC. Our study shows that 32% of the patients who were recommended to receive AC rejected the treatment and elected to be monitored instead. Patients who undergo a curative treatment for MIBC in the form of RC might be more reluctant to receive additional treatment. The associated morbidity brought by such a major surgery alone would interfere with the initiation of AC. On the other hand, patients who were offered NAC were more willing to initiate treatment to improve their chance for a cure as well as survival (88.6%).

Furthermore, among patients who initiated perioperative chemotherapy, NAC patients were more likely to complete the number of planned cycles (94.4%), while only 52.7% completed the AC treatment.

Currently, NAC followed by RC is an established approach for MIBC. Supported by several randomized trials, NAC is associated with a survival benefit of 6.5% and a lower risk of BC-specific mortality. On the other hand, the survival benefit with AC is controversial. Our study shows that patients are more likely to accept and complete NAC, and this further supports the administration of NAC for MIBC.

Our study has some limitations. Chemotherapy protocols were not the same throughout the study period as novel chemotherapy regimens with less toxicity became available. However, the protocols offered were the same in the NAC and AC setting at a specific time. This study is limited to the likelihood of initiation and completion of NAC and AC. The benefits and side effects of chemotherapy are beyond the scope of this study.

### Table 2: Reasons for not initiating/completing the chemotherapy

| Reason for not initiating/completing | NAC N 141 (%) | AC N 222 (%) |
|--------------------------------------|--------------|--------------|
| Patient preference                    | 16 (100)     | 15 (21.0)    |
| Surgical/medical condition            | N/A          | 56 (79.0)    |
| Reason for non-completion             | 7            | 72           |
| Renal impairment                      | 2 (28.5)     | 9 (12.5)     |
| Intolerability                        | 3 (43.0)     | 23 (32.0)    |
| Hematological complications           | 2 (28.5)     | 33 (46.0)    |
| Sepsis                                | 0            | 7 (9.5)      |

### CONCLUSION

Patients with MIBC are more likely to initiate and complete the planned number of cycles of neoadjuvant chemotherapy as compared to adjuvant chemotherapy. Therefore, we advocate administration of chemotherapy in the neoadjuvant setting in patients who are likely to benefit from chemotherapy.

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