Administration of neoadjuvant chemotherapy for muscle-invasive bladder cancer in real life: Are urologists still too cautious?

Administration de chimiothérapie néoadjuvante pour tumeur de vessie infiltrant le muscle en vie réelle : les urologues encore trop frileux ?

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Chemotherapy; Adjuvant; Neoadjuvant therapy; Urinary bladder neoplasms

Summary
Introduction. — Neoadjuvant chemotherapy (NAC) is now recommended to treat muscle-invasive bladder cancer (MIBC) but is not always executed in real life. This study aims to evaluate the proportion of patients with MIBC who receive an optimal NAC, and to present the predictive factors of its achievement.

Methods. — This monocenter retrospective study included all the patients who underwent radical cystectomy for ≥pT2NxM0 MIBC between 2013, January and 2018, December. NAC consisted in 4–6 cycles of MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) or 4 cycles of GC (gemcitabin, and carboplatin). Demographic (sex, age, ECOG-PS, glomerular filtration rate [GFR], and cN stage), surgical (urinary derivation, time of surgery, blood loss, and complications), and oncological characteristics were analyzed. Multivariate analysis are made to find predictors of administration of NAC.

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Results. — One hundred and twenty-seven patients were included. Thirty received CNA (24%). Patients who underwent CNA were younger, with better ECOG and better GFR. Multivariate analysis showed that C/N+ stage and better GFR were significantly associated to administration of NAC. Eight patients (27%) couldn’t receive an optimal treatment due to toxicity. Perioperative complication rates were similar, with or without NAC. Patients who underwent NAC had a worse GFR after treatment (−17 versus +5 mL/min, P < 0.01).

Conclusion. — Due to the risks of toxicity, NAC can only be proposed to selected population, which is not the current patients. Immunotherapy could allow to treat more patients because of better tolerance.

Level of evidence. — 3.

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Résumé

Introduction. — La chimiothérapie néoadjuvante (CNA) est recommandée dans le traitement des tumeurs de vessie infiltrant le muscle (TVIM), mais n’est pas toujours réalisée en pratique. L’objectif était d’évaluer le pourcentage de patients atteints d’une TVIM localisée recevant une CNA optimale, et d’identifier les facteurs prédictifs de sa réalisation.

Méthodes. — Il s’agit d’une étude rétrospective, monocentrique, incluant les patients opérés d’une cystectomie pour TVIM localisée entre janvier 2013 et décembre 2018. La CNA consistait en 4 à 6 cures de MVAC intensifié (méthotrexate, vinblastine, doxorubicine, et cisplatine) ou de GC (gemcitabine, et cisplatine). Les caractéristiques démographiques (sexe, âge, ECOG-PS, débit de filtration glomérulaire [DFG], et stade C/N), chirurgicales (dérivation urinaire, durée opératoire, pertes sanguines, et complications périopératoires) et carcinologiques étaient analysées. Les facteurs prédictifs d’administration de la CNA étaient recherchés en analyse multivariée.

Résultats. — Cent-vingt-sept patients ont été inclus, dont 30 ont reçu une CNA (24 %). Les patients traités par CNA étaient plus jeunes, avec un meilleur ECOG et un meilleur DFG. En analyse multivariée, le statut ganglionnaire C/N+ et un meilleur DFG étaient significativement associés à la probabilité d’avoir une CNA. Huit patients (27 %) n’ont pas pu recevoir la totalité du traitement pour toxicité. Le taux de complications périopératoires était similaire avec ou sans CNA. Les patients traités par CNA avaient une diminution plus importante de leur DFG (−17 versus +5 mL/min, p < 0.01).

Conclusion. — En raison du risque de toxicité, la CNA ne peut être proposée qu’à une population sélectionnée. Cela ne correspond pas aux patients rencontrés en pratique courante. Les immunothérapies pourraient permettre de traiter plus de patients.

Niveau de preuve. — 3.

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Introduction

In France, bladder tumors had an incidence of more than 13,000 new cases in 2018 and are responsible for 5300 deaths per year (Santé publique France 2019). At the time of diagnosis, 25 to 30% of bladder tumors have infiltrated the muscle [1], and up to 30% of tumors that do not infiltrate the muscle later become secondarily infiltrating tumors [2]. The standard treatment for localized muscle-invasive bladder cancer (MIBC) is neoadjuvant chemotherapy (NAC) based on cisplatin, in the absence of contraindication prior to radical cystectomy with extensive pelvic lymph nodes dissection [3]. Since the randomized trial published by Grossman et al. in 2003 [4], several meta-analyses have confirmed the benefit of NAC, regardless of the initial stage of MIBC, with an improvement in five-year survival of 8% [5]. Therefore, NAC is recommended for patients with good renal function (glomerular filtration rate usually greater than 60 mL/min) and in good general condition [3].

Despite a large amount of evidence, the use of NAC remains limited, with approximately 20% of patients receiving treatment before cystectomy in the United States [6]. Among the concerns raised, toxicity of chemotherapy, delay in performing the surgery and possibility of more important operative complications have been put forward. However, only poor data from France on the use of NAC in real life are available. The aim of this single-center study was to present the proportion and characteristics of patients receiving NAC prior to cystectomy for localized MIBC.
Methods

Population

This study was a single-center, retrospective study including all patients who underwent cystectomy for urothelial bladder carcinoma ≥ pT2NxM0 between January 2013 and December 2018. The diagnosis of MIBC was based on the pathological analysis of the trans-urethral resection of bladder tumor (TURBT). Patients with infiltrating bladder tumors whose analysis showed another histology than urothelial carcinoma were excluded. Patients who received another type of neoadjuvant therapy (immunotherapy in a clinical trial) were also excluded. Extension evaluation included pelvic-abdominal and chest CT-scan, without and with injection of contrast product when the patient’s renal function allowed it, or a chest CT-scan without injection and an abdominal and pelvic MRI otherwise. Every CT-scans were read by an onco-urologist-radiologist. Therapeutic strategy was discussed collegially in a multidisciplinary meeting in accordance with national committee CC-AFU guidelines.

Treatment

NAC consisted in four to six cures of high-dose MVAC (methotrexate 30 mg/m² on day one, vinblastin 3 mg/m² on day one, doxorubicin 30 mg/m² on day one and cisplatin 70 mg/m² on day one with hydrier from before and after administration, every two weeks) or three to four cures of GC (gemcitabine 1000 mg/m² on day one, day eight and cisplatin 70 mg/m² on day one with hydrier from before and after administration, every three weeks). Safety was assessed before each injection by a medical oncologist. A reassessment chest and abdomino-pelvic CT-scan was performed at the end of NAC.

Surgical treatment consisted in radical cystectomy (for men: removal of the bladder, prostate, seminal vesicles; for women: removal of the bladder, entire urethra, adjacent vagina and uterus) with ilio-obturator, external iliac, internal iliac and primary iliac dissection up to the crossing of the ureters. Type of urinary diversion was decided by the surgeon in agreement with the patient (transileal cutaneous ureterostomy [Bricker], neobladder or ureterocutaneousostomies). Ureteral and urethral resections were sent for extemporaneous intraoperative analysis. Histological analysis was performed by an uropathologist. Surgical complications occurring during the hospital stay were classified according to the Clavien-Dindo classification [7]. The clinical and radiological monitoring of patients was classically organized at months three, six and twelve, then every six months for at least five years.

Statistical analysis

Demographic (sex, age, ECOG/WHO-PS, glomerular filtration rate [GFR], and cN stage), surgical (urinary diversion, surgery time, blood losses, and intra- and post-operative complications) and oncological (progression and death) outcomes were analyzed. Qualitative variables were compared using the χ² test and Fisher’s exact test. Quantitative variables were compared by the Wilcoxon test and the Kruskal-Wallis test. Survival curves were generated according to the Kaplan-Meier method and compared by the log-rank test. Predictors of NAC administration were sought in a multivariate analysis using a logistic regression model. A P<0.05 was considered statistically significant. Every analysis was carried out with R software version 3.6.1 (https://cran.r-project.org).

Results

Population characteristics

Between 2013 and 2018, 1290 patients were treated for urothelial tumors in our center, with an average of 215 patients per year. Over the same period, an average of 35 cystectomies per year were performed. A total of 127 patients were included in this study: 30 patients (23.6%) received NAC before surgery, and 97 patients (76.4%) were treated with surgery only. Characteristics of the population were summarized in Table 1. Median age at diagnosis was 73.0 years (66.0—79.5), and 85.8% of the patients were men. Patients treated with NAC were significantly younger (66.5 versus 75.0 years, P<0.001), with a better ECOG-PS score (90.0% versus 62.9% of ECOG 0 patients, P=0.016) and better renal function (GFR 78.5 versus 56.0 mL/min, P<0.001). Twenty patients (15.7%) presented pelvic lymph nodes ≥ 1 cm on the extension evaluation (cN+), with a bigger proportion in the group treated with NAC (43.0% versus 7.2%, P<0.001).

NAC methods

Among the 30 patients who received NAC, 22 (73.3%) were able to undergo full treatment, and eight patients (26.7%) could not have received all the chemotherapy due to occurrence of toxicities: one grade 4 complication (rectal bleeding complicated by septic and hemorrhagic shock), three grade 3 complications (severe infection, dental abscess, and hearing loss, respectively) and three grade 2 complications (two acute renal failure and neuropathy). For one patient, the cause of the premature cessation of chemotherapy was not known, because it was carried out in another center. The reasons for not performing neoadjuvant chemotherapy are listed in Table 2. Decreased renal function (GFR<60 mL/min) was the main reason for refusing NAC (46.4% of patients). For almost a quarter of the patients (23.7%), no objective cause of refusal of NAC was found. Among the 30 patients treated with NAC, 25 (83.3%) received an MVAC protocol, four (13.3%) received a cisplatin-gemcitabine combination and one (3.3%) received a carboplatin-gemcitabine combination. Distribution of patients according to their treatment modality was shown in Fig. 1. Between 2013 and 2018, the proportion of patients receiving NAC with cystectomy varied from 13.0% to 33.0% (Fig. 2), but any increasing trend was identified. In multivariate analysis, cN+ lymph node status and higher GFR were significantly associated with the occurrence of NAC (Table 3).
Surgical management

Delay between diagnosis and cystectomy was 58.0 days [41.0–83.0] in the surgery group and 126.0 days [110.0–154.0] in the NAC group, with a median time of 37.4 days [32.0–46.0] between the end of chemotherapy and surgery. Time between diagnosis and the start of active treatment was comparable in the two groups (58.0 versus 43.0 days, P = 0.135). No significant difference was found concerning the operating duration (330 versus 300 min, P = 0.325), rate of surgical complications (48.5% versus 50.0%, P = 0.884) or length of hospitalization (16.0 days in each group, P = 0.087). Intraoperative blood losses were lesser (600 versus 500 mL, P = 0.019) in the surgery only group. One month after cystectomy, the patients treated with NAC had a greater decrease in their GFR (−17 versus +5 mL/min, P < 0.01), despite a comparable rate of perioperative complications between the two groups (48.5% versus 50.0%, P = 0.884). There was no significant difference in the occurrence of urinary anastomosis stenosis which needed to replace a unilateral or bilateral ureteral catheter, or a neobladder catheter (12.4% versus 10.0%, P = 1.0).

Oncological results

Radiological reassessment at the end of NAC showed 23.0% of the patients with a complete response, 33.0% of the patients with a partial response, and 37.0% of the patients with a
Table 2  Refusal of NAC: causes.

<table>
<thead>
<tr>
<th>Causes</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years-old</td>
<td>42 (43.3%)</td>
</tr>
<tr>
<td>GFR &lt; 60 mL/min</td>
<td>45 (46.4%)</td>
</tr>
<tr>
<td>ECOG/WHO-PS &gt; 1</td>
<td>7 (7.2%)</td>
</tr>
<tr>
<td>Patient’s medical history</td>
<td>12 (12.4%)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>23 (23.7%)</td>
</tr>
</tbody>
</table>

stable disease, according to RECIST criteria. No progression with treatment has been reported. Pathological analysis of the cystectomy specimens found residual disease (>pT2) in 83.5% of patients treated with prior surgery versus 44.8% of patients treated with NAC (P<0.01). The rate of pN+ patients was comparable in the two groups (37.1% versus 33.3%, P=0.746). Twenty-three patients (18.1%) received adjuvant chemotherapy, including four in the NAC group. After a median follow-up of 21.6 months [9.9–35], 50 patients (39.3%) had progressed, and 34 (26.7%) had died. Fig. 3 represents the survival curves between the two groups. NAC was associated with a decreased risk of progression (HR = 0.44, [0.21; 0.94], P = 0.03), with no statistically significant benefit on overall survival (HR = 0.52, [0.22; 1.27], P = 0.14).

Discussion

Despite a proven benefit in overall survival, with a high level of evidence [5], the use of neoadjuvant chemotherapy in real life remains limited in patients with localized MIBC. In this single-center series, less than a quarter of the patients started neoadjuvant chemotherapy, and, of these, another quarter did not receive full treatment due to toxicity reasons. European and American data show a comparable underuse of NAC, with approximately 20% of patients treated [6,8,9]. There are several reasons for this situation. First, 57% of the patients in this study had contraindications to the administration of cisplatin-based chemotherapy. In the literature, approximately half of patients are not eligible for treatment due to renal failure (GFR < 60 mL/min), poor general condition (ECOG-PS ≥ 2), heart failure, neuropathy or hypoacusis (grade ≥ 2).
These patients could theoretically receive treatment with carboplatin, but several trials in a metastatic situation have shown poorer efficacy compared to cisplatin, and its benefit at the localized stage has never been demonstrated [12]. Therefore, in a non-metastatic situation, the use of carboplatin-based chemotherapy remains limited to patients with locally advanced disease or cN+ as part of primary chemotherapy. There is currently a therapeutic gap for patients who are ineligible for cisplatin in a neoadjuvant situation.

Although the patients treated with NAC were significantly younger, with better general health and better renal function, more than a quarter of these patients were unable to complete treatment due to chemotherapy-related toxicities, including half of severe complications (grade 3–4). Other studies have found similar complication rates [13–15]. This high rate of complications may explain the reluctance to administer NAC if the complications lead to a deterioration of the general condition, preventing surgery. For 23% of patients, analysis of the file did not find an objective contraindication to the NAC. Therefore, it seems that some patients, who could in theory benefit from this treatment, ultimately do not have access to it. Similar rates are found in the literature [13] and could be explained in part by the underestimation of symptomatic patients with persistent hematuria or disabling lower system symptoms. These symptomatic forms leading to an initial cystectomy represent between four and 20% of cases in the literature [16]. However, there is also surgical reluctance to use NAC, particularly because of the risk of toxicity. One of the concerns raised is the delay in carrying out curative treatment by cystectomy, especially in patients who do not respond to chemotherapy. A delay between MIBC diagnosis and cystectomy greater than 12 weeks is associated with decreased survival in the absence of NAC [17,18]. Nevertheless, a more recent study has shown that, subject to initiating NAC within seven weeks of diagnosis, the time to surgery had no effect on survival, including in patients who did not respond to NAC [19]. However, when the time between the end of chemotherapy and cystectomy exceeds twelve weeks, the risk of lymph node invasion is significantly increased [20]. In our series, the median time from the end of chemotherapy to surgery was 5.3 weeks. A greater risk of perioperative complications after NAC has also been suggested. In our study, no significant difference was found concerning the operating duration, rate of surgical complications or length of hospitalization. Blood loss was even lower in the group treated with NAC. Other retrospective studies have also shown that NAC does not induce additional surgical morbidity [21]. However, not all patients benefit from NAC, and the pathological response rate ≤ pT1 was 55% in our series. In the literature, the response rate after NAC is between 20 and 40% and is associated with a significant improvement in survival [22,23].
Several biomarkers of response to chemotherapy are currently being evaluated, including certain mutations [24–26] or molecular subtypes [27], to select the patients most able to respond and avoid treating non-responsive patients. The impossibility of a systematic analysis of molecular subtypes in routine is currently a major limitation preventing the selection of patients according to this criterion. Due to the lack of centralized reading of slides in our center, it is not possible to know for all patients the hypothetical presence of histological variants with poor prognosis. This could also be an additional argument in favor of the administration of neoadjuvant chemotherapy; however, there is currently no formal argument in the literature in favor of this hypothesis.

The future of neoadjuvant therapy in MIBC may hinge on immunotherapy. Clinical trials evaluating checkpoint inhibitors alone or in combination with chemotherapy are underway. The results of 2 phase II studies with atezolizumab (ABACUS) or pembrolizumab (PURE-01) conducted in 95 and 50 patients with localized MIBC show a pathological response rate of 31 and 42%, respectively, with a more favorable safety profile [28,29]. The development of biomarkers could make possible in the future to better select patients who are candidates for neoadjuvant therapy while avoiding potential adverse effects in non-responder patients. If their efficacy is confirmed in the phase III setting, immunological checkpoint inhibitors could make it possible to treat a larger number of patients.

This single-center retrospective study has several limitations. First, the workforce remains relatively small. Second, the causes of NAC refusal were not found for all patients. This led us to believe that there was still reluctance to administer NAC. This hypothesis is also suggested by the absence of an increase in the rate of patients treated with NAC in our center in recent years, contrary to the data in the literature on the subject [30]. Finally, the patients included in this study underwent radical cystectomy for MIBC. Among these patients, a number had a CN+ disease, and chemotherapy was more like induction chemotherapy than neoadjuvant chemotherapy. However, the results of this real-life study are consistent with data in the literature and suggest the underuse of NAC.

Conclusion

NAC is recommended in the treatment of localized MIBC before cystectomy, in the absence of contraindication, as it provides a benefit in survival. However, our real-life data show that a minority of patients, namely, those who are younger and in better condition, benefit. In addition, almost a quarter of patients have not received treatment in the absence of an objective contraindication, suggesting that there is still a significant reluctance to use NAC. These results confirm the need to sensitize the urological community to the oncological benefits of NAC in the absence of contraindications.

Disclosure of interest

The authors declare that they have no competing interest.


