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Neoadjuvant Chemotherapy for Urothelial Muscle-Invasive Bladder Cancer: Influence of Body Mass Index on Efficacy and Toxicity

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1. Abstract

1.1. Background: Neoadjuvant Chemotherapy (NAC) and radical cystectomy with pelvic lymph node dissection are the cornerstone of therapy for patients with Muscle Invasive Bladder Cancer (MIBC). We assessed the potential influence of body mass index (BMI) on toxicity and efficacy of NAC in patients with MIBC.

1.2. Patients and Methods: Treatment duration, toxicity and efficacy of NAC were compared between obese patients receiving chemotherapy based on capping at a body-surface area of 2.2 m^2 and healthy weight patients. Obese patients were individually paired with normal BMI patients sharing similar clinical and biological characteristics.

1.3. Results: Twenty-seven (20%) of 124 patients were categorized as obese. The median number of NAC cycles was 5 whatever the BMI subgroups. No significant difference regarding toxicity was observed. The pathological complete response rates were similar.

1.4. Conclusion: Capping the body-surface area at 2.2 m^2 in obese patients does not jeopardize the tolerance and efficacy of NAC in MIBC.

2. Introduction

Patients with clinically localized, Muscle-Invasive Bladder Cancer (MIBC) are managed in a curative setting. Neoadjuvant Chemotherapy (NAC) and radical cystectomy with pelvic lymph node dissection represent the cornerstone of therapy. The benefit of NAC on overall survival has been shown with cisplatin-based regimens [1, 2]. Currently used drug combinations are based on Methotrexate, Vinblastine, Doxorubicin and Cisplatin (MVAC) or Gemcitabine Plus Cisplatin (GC). With increasing rates of obesity worldwide, more patients that are overweight are likely to receive NAC for MIBC. Uncertainty remains among physicians regarding the optimal drug dosing in the population of overweight and obese patients [3-5]. As the influence of BMI has never been studied so far for patients treated with NAC for MIBC, we undertook a retrospective study in patients who received dose-dense MVAC (dd-MVAC) in our institution, with the objective of evaluate the impact of Body Mass Index (BMI) on treatment delivery, toxicity and efficacy of NAC.

3. Patients and Methods

3.1. Patients and Treatments

From January 2011 to August 2018, 134 patients were treated with dd-MVAC as NAC in our institution. All patients had histologically proven urothelial MIBC with clinical and radiological evidence of T2-4a, N0-N1, M0 disease, and a calculated glomerular filtration rate of 60 mL/minute or greater. Clinical T stage was defined by transurethral biopsy samples. Radiologic assessment by computed tomography scan or magnetic resonance imaging was used

to determine clinical N stage. Chemotherapy consisted of methotrexate 30 mg/m^2 IV on day (d) 1, vinblastine 3 mg/m^2 IV on d2, doxorubicin 30 mg/m^2 IV on day 2, and cisplatin 70 mg/m2 on d2 with hydration before and after administration, each cycle every 2 weeks with prophylactic GCSF for 7 days, starting 24 hours after the last dose of cytotoxic drug. Body Surface Area (BSA) was calculated using the DuBois and Dubois formula: BSA (m^2) = 0.007184 x height (cm)$^{0.725}$ x weight (kg)$^{0.425}$. BSA was routinely caped at 2.2 m^2. Dose reductions in case of toxicity were as followed: the cisplatin dose was adapted to renal function (50 mg/m^2 for creatinine clearance between 50 and 59 ml/mn, 40 mg/m^2 between 40 and 49 ml/mn). A 15% dose reduction for other drugs was also recommended in case of grade 4 extra-renal toxicity. The planned number of cycles was 6, although chemotherapy could be discontinued prematurely at the discretion of the treating physician in case of excessive toxicity or disease progression. Clinical toxicities and significant laboratory values were prospectively documented at the beginning of each chemotherapy cycle. Radical cystectomy was planned for approximately 4-6 weeks after the final cycle of chemotherapy.

3.2. Methodology

Body Mass Index (BMI) was calculated using the weight in kg divided by the square of the height in meters. Patients were classified into subgroups according the definition of The World Health Organization: normal (18.5 to < 25 kg/m^2), overweight (≥ 25 to < 30), obese (≥ 30) and morbidly obese (≥ 40) [5]. Twenty-seven (20%) of 124 patients were categorized as obese (Table 1). None was classified as morbidly obese. Each obese patient was paired with a normal BMI patient sharing similar clinical (age, sex, smoking status, stage, histology, performance status) and biological (albumin, creatinine clearance) characteristics. Therefore, the only difference between the two groups of obese versus non-obese patients was BMI (Table 2). Toxicities of NAC were retrospectively graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) based on individual medical reports. The efficacy endpoint was the rate of pathological Complete Response (pCR), defined as the absence of residual disease on cystectomy specimens (ypT0N0 stage).

Table 1: Study population according to body mass index

Group	Body Mass Index (kg/m2)	Patients (%)
Thin	< 18.5	8 (6%)
Normal	18.5 – 24.9	50 (37%)
Overweight	25 – 29.9	49 (36%)
Obese (level I)	30 – 34.9	22 (16%)
Obese (level II)	35 – 39.9	5 (4%)
Morbidly obese (level III)	≥ 40	0

Table 2: Patients' characteristics

Parameter	Normal (N=27)	Obese (N=27)
BMI (median, kg/m2)	23	31
Age (median, years)	67	69
Sex (H/F)	24/3	24/3
Smoking status		
Non smoker	5	3
Former smoker	11	17
Current smoker	11	7
Performance status		
0	19	21
1	8	6
Histology		
Urothelial pure	18	20
Urothelial with variants	9	7
Stage		
T2 N0	15	15
T3 N0	3	3
T4 N0	2	2
Tx N1	7	7
Albumine (median, g/L)	40	41
Creatinine clearance (median, mL/mn)	90	80

4. Results

4.1. Treatment Delivery

The median number of dd-MVAC cycles was 5 whatever the BMI subgroups. Just under half of the patients received 6 cycles. Dose reductions during the course of chemotherapy was required in 10 (37%) obese patients and 13 (48%) patients with normal BMI (Table 3). If BSA had not been capped at 2.2 m^2, 6 patients with BSA ranging from 2.3 to 2.7 m^2 would have received higher chemotherapy doses. Two of them required dose reductions.

Table 3: Treatment delivery

	Normal (N=27)	Obese (N=27)	p value
Number of cycles (median)	5	5	NS
Number of patients who received 6 cycles	13 (48%)	12 (44%)	NS
Total dose of cisplatin (median, mg)	350	350	NS
Number of patients without dose reduction (%)	13 (48)	10 (37)	NS

4.2. Toxicity

Grade 3/4 toxicities are reported in Table 4. No significant difference was observed according to BMI subgroups. Overall at least one episode of grade 3 or 4 biological or clinical toxicity was observed in 17 (63%) and 16 (59%) of patients with an obese and normal BMI, respectively.

Table 4: Severe (grade 3/4) toxicities

Parameter	Normal (N=27)	Obese (N=27)	p value
Neutropenia (%)	8 (30)	7 (26)	NS
Febrile neutropenia (%)	3 (11)	1 (4)	NS
Thrombocytopenia (%)	5 (18)	4 (15)	NS
Anemia (%)	9 (33)	5 (18)	NS
Kidney injury (%)	1 (4)	1 (4)	NS
Asthenia (%)	10 (37)	8 (30)	NS
Nausea/Vomiting (%)	1 (4)	3 (11)	NS
Mucositis	3 (11)	4 (15)	NS
Peripheral neuropathy (grade 2, %)	2 (8)	1 (4)	NS
Ototoxicity (grade 1-2, %)	5 (18)	3 (11)	NS
Cardiovascular	0	0	
Toxic death	0	0	

4.3. Efficacy

After NAC, radical cystectomy was performed in 24 (89%) patients with initial normal BMI and 21 (78%) obese patients. The pCR rate was similar in both groups. The reasons for not performing cystectomy in 10 patients are shown in Table 5. Seven of them underwent bladder-sparing treatment with chemo-radiotherapy. Disease progression occurred in only one (obese) patient. Among 6 patients who received suboptimal doses because of capping of BSA at 2.2 m^2, only 3 were operated on without reaching a pCR status, while 2 patients received chemo-radiotherapy and 1 refused any kind of local treatment.

Table 5: Efficacy

	Normal (N=27)	Obese (N=27)
Radical cystectomy	24	21
Pathological complete response	12 (50%)	11 (52%)
Reasons for not performing surgery		
Patient refusal	0	1
Patient and/or physician preference	3	4
Progressive disease	0	1

5. Discussion

In adult patients with cancer, dosing of cytotoxic drugs has traditionally been based on a patient's estimated BSA [6]. For fear of excessive toxicity, many oncologists continue to cap the BSA rather than use actual body weight to calculate BSA. In practice pattern studies, up to 40% of obese patients have been reported to receive suboptimal doses of cytotoxic drugs [7]. In the present study, only 6 of 27 (22%) patients were not treated with full weight-based doses. Would the BSA have been capped at 2 m^2, 14 (52%) patients would have actually received suboptimal doses. As there is compelling evidence that reductions from standard dose and dose-intensity may compromise overall survival in a curative setting [8] such as MIBC, we wanted to assess the impact of the capping at 2.2 m^2 used in the last decade. The results seem reassuring since we have not highlighted any difference between obese patients and a subgroup of paired patients with similar clinical and biological characteristics.

However, this study has several limitations, including first its retrospective design and its small size. The observation that no pCR was observed among 6 patients who did not receive full weight-based doses remains inconclusive as only 3 of them underwent surgery. Another way to approach the BMI issue would have been to compare the subgroup of obese patients to the whole population of patients with BMI < 30 kg/m^2. Yet such a methodology would have introduced more heterogeneity and therefore a lower power in comparing subgroups of patients. Finally, survival results were not used considering the small sample size of patients. However, a strong relationship between pCR rate and overall survival has been established in patients with MIBC [9].

The influence of BMI has never been studied so far for patients treated with NAC for MIBC. Only one previous study assessing the impact of obesity on outcomes of patients with bladder cancer was reported in metastatic disease [10]. Data from 537 patients included in a number of phase II and phase III clinical trials investigating first-line cisplatin-based chemotherapy were aggregated. No significant difference in adverse events or survival outcomes was observed across BMI and BSA categories, except for higher incidences of embolic events and renal failure in patients with an average or higher BSA. However, the BSA capping policy used in studies was not reported.

The panel of experts who wrote practice guideline for the American Society of Clinical Oncology in 2012 recommended further research into the role of pharmacokinetics and pharmacogenetics to optimize dosing in obese cancer patients [7]. Unfortunately, no study has been reported with the dd-MVAC regimen so far. When we consider the pharmacokinetics of each drug involved in this combination, a significant increase in the absolute clearance of cisplatin has been shown in obese patients, likely related to an increase in tubular secretion [11]. Results for doxorubicin are less clear since the systemic clearance was significantly reduced in obese women, but not in obese men [11]. The association between BMI and outcomes in women treated with the combination of doxorubicin and cisplatin for advanced or recurrent endometrial cancer was studied by the Gynecologic Oncology Group. As compared to dd-MVAC, cisplatin doses were slightly inferior (50 to 60 mg/m^2/cycle) while doxorubicin doses were twice higher (60 mg/m^2/cycle). Among 949 patients enrolled into 5 prospective studies, 43.4% were obese. No significant associations between BMI and progression-free survival were detected. Obese patients had less grade 3/4 toxicities, probably secondary to BSA capping at 2 m^2 [12].

In conclusion, treating obese patients with BSA capped at 2.2 m^2

does not appear to jeopardize the tolerance and efficacy of NAC in MIBC in our experience. Beyond this threshold, consideration of comorbid conditions seems important before using full weight-based chemotherapy dosing.

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