Optimizing immunotherapy in locoregional and metastatic urothelial cancer

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Part I

Checkpoint immunotherapy in metastatic urothelial cancer

2

Response rate to chemotherapy after immune checkpoint inhibition in metastatic urothelial cancer

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are active in metastatic urothelial carcinoma (MUC). They have joined chemotherapy (CT) as a standard of care. Here, we investigate the activity of CT after progression on ICIs. Two cohorts of sequential patients with MUC were described (n = 28). Cohort A received first-line ICIs followed by CT after progression. Cohort B received CT after failure of first-line platinum-based CT followed by ICIs. Response rate (RR) to CT was assessed using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) by a designated radiologist. Best RR for cohort A was 64%. Two patients experienced clinical progression and died before the first radiographic assessment. RR for cohort B was 21%, which was significantly lower than that for cohort A. Progression of disease occurred in 43% of cohort B patients by the end of CT. These data suggest a lack of cross resistance between CT and ICIs in MUC. Therefore, the sequencing of these drugs is likely to be important to maximize outcomes. This is particularly true after first-line ICIs as subsequent CT has significant activity.

Patient summary

In this report, we studied the effect of chemotherapy in metastatic bladder cancer, which relapsed after immune checkpoint inhibitors. We found that the activity of chemotherapy was maintained despite previous exposure to immune therapy. This underlines the importance of sequencing these agents to maximize outcomes.

INTRODUCTION

Metastatic urothelial carcinoma (MUC) is largely incurable and the mortality rates have not changed substantially over the past 2 decades (1). Treatment until recently has been focused on chemotherapy (CT). Platinum-based combination CT is considered standard of care for treatment-naive patients (2,3). The response rates for these regimens range between 40% and 50%. Second-line CT regimens have disappointing results, and there is no clear consensus on standard of care (4). Therefore, cross resistance between CT regimens in the first- and second-line settings exists.

A number of immune checkpoint inhibitors (ICIs), targeting the PD-L1/PD-1 axis, have been investigated successfully in both the platinum refractory and the previously untreated setting (5). Response rates are approximately 20% in both scenarios. While cross resistance occurs when sequencing CT regimens in MUC, it remains unclear if cross resistance occurs when sequencing CT and ICIs. This is particularly relevant in patients who are treated with first-line ICIs, where a large proportion of patients progress quickly (6,7). If CT is subsequently active in these patients, it would underline the importance of sequencing these drugs to maximize outcome. In this work, we explore the response rates of CT in MUC patients who progress after ICIs. A comparison of the response rates of patients who received third-line treatment (after CT and ICIs) and second-line treatment (after only ICIs) was made.

METHODS

An audit on patients with MUC previously treated with ICIs (PD-1/PD-L1) was performed based on the data from the databases of two institutions (Barts Health, London, and Netherland Cancer Institute, Amsterdam). All patients had measurable, metastatic, histology-proven disease and received at least one cycle of CT after ICI therapy.

Patients were divided into two cohorts (Fig. 1A):

1. Cohort A: The CT-naive group. This group received first-line ICIs upon diagnosis of MUC. After demonstration of progression of disease on ICIs, they received standard CT.
2. Cohort B: The CT-resistant group. This group was treated with standard CT after previously receiving the sequence of first-line CT followed by second-line ICIs.

The primary objective was to report the response rates of CT in MUC in cohorts A and B. Response rate was based on Response Evaluation Criteria in Solid Tumors (RECIST

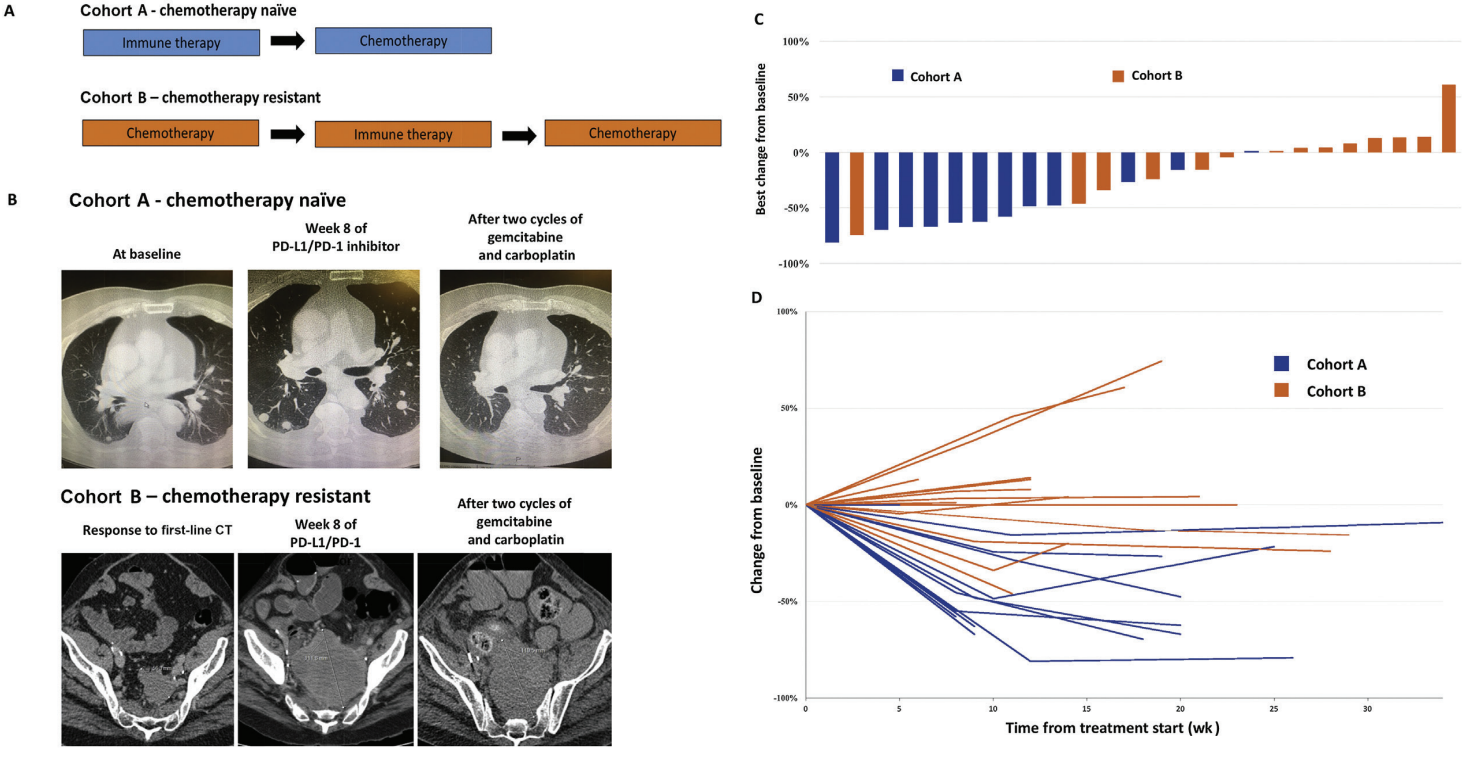

Fig. 1 – **(A)** Study cohorts. **(B)** Response patterns in cohorts A and B. **(C)** Best change in tumour burden. Measurement was performed as per RECIST v1.1. The two patients who died prior to imaging were not included in this analysis. **(D)** Change from baseline tumour burden, defined as the sum of target lesion diameters over time.
CT = chemotherapy; RECIST = Response Evaluation Criteria in Solid Tumors.

v1.1). Imaging was re-reviewed by a designated radiologist. The two patient groups were compared using descriptive statistics. Appropriate ethical approvals were in place. Baseline clinicopathological characteristics and clinical follow-up data are given in Table 1. Patients received a PD-1 inhibitor, a PD-L1 inhibitor, or a combination of both as their immediate previous therapy. Details on these ICI regimens are not given as the patients participated in clinical trials. The patients followed established standard of care pathways for CT. They underwent tumor assessments with cross-sectional imaging every 8 weeks after starting with CT treatment. This work focused on the time from starting CT after progression on ICIs. The patients were stratified according to the Bajorin risk factors into favorable-, intermediate-, and poor-risk groups (8).

RESULTS

Twenty-eight patients with MUC who received CT after progression on ICIs were identified. Median follow-up was 8.2 mo (interquartile range [IQR] 6.5–11.3 mo). In each cohort 86% of patients had visceral metastatic disease. In cohort B, the most common first-line CT regimen was gemcitabine and cisplatin (n = 11). Other regimens are given in Table 1. The median numbers of cycles were 6 (IQR 5–6) and 4.5 (IQR 4–6), with a median duration of 16 (IQR 13–18) and 14 (IQR 10–16) wk in cohorts A and B, respectively. Response rates to first-line CT before ICIs in cohort B were 57%, which is in line with those described previously (2,3).

In cohort A, nine (64%) patients had partial remission as the best response rate. Three (21%) showed stable disease (Table 1, Fig. 1B and 1C), and two patients (14%) had early progression of disease and died prior to imaging. These two patients had intermediate-risk disease and each died after one cycle of CT (Fig. 1A and 1B).

In cohort B, three patients (21%) showed partial response, 10 (71%) achieved stable disease, and one (7%) progressed as the best response to CT. Progression of disease at the completion of CT was 14% in cohort A and 43% in cohort B.

Table 1. Baseline characteristics and best overall response rates as per RECIST v1.1 of patients in cohorts A and B

Characteristics	Cohort A, n (%) (n=14)	Cohort B, n (%) (n=14)
Median age (IQR), yr	68 (51-80)	56 (34-79)
Sex		
Male	11 (79%)	6 (43%)
Female	3 (21%)	2 (14%)
ECOG		
0	3 (21%)	5 (36%)
1	8 (57%)	9 (64%)
2	3 (21%)	0
Baseline haemoglobin, g/dl		
≥10	8 (57%)	6 (43%)
<10	6 (43%)	8 (57%)
Metastatic sites at baseline		
Lung	9 (64%)	8 (57%)
Liver	6 (43%)	5 (36%)
Bones	5 (36%)	5 (36%)
LN	13 (93%)	11 (79%)
LN only	2 (14%)	2 (14%)
Number of organs involved		
1	2 (14%)	4 (29%)
2	4 (29%)	5 (36%)
≥3	8 (57%)	5 (36%)
Prior treatment		
Cystectomy	4 (29%)	9 (64%)
Radiotherapy	0	3 (21%)
Presenting with metastatic disease		
No	8 (57%)	11 (79%)
Yes	6 (43%)	3 (21%)
Bajorin risk group		
0	2 (14%)	2 (14%)
1	9 (64%)	12 (86%)
2	3 (21%)	0
Chemotherapy regimen pre-ICI		
Gembitabine/cisplatin		11 (79%)
Gemcitabine/carboplatin		1 (7%)
Paclitaxel/carboplatin		1 (7%)
MVAC		1 (7%)

Table 1. Baseline characteristics and best overall response rates as per RECIST v1.1 of patients in cohorts A and B *(continued)*

Characteristics	Cohort A, n (%) (n=14)	Cohort B, n (%) (n=14)
Chemotherapy regiment post-ICI		
Gembitabine/cisplatin	4 (29%)	1 (7%)
Gemcitabine/carboplatin	10 (71%)	3 (21%)
Paclitaxel/carboplatin	0	7 (50%)
Docetaxel	0	3 (21%)
Best overall response		
CR	0	0
PR	9 (64%)	3 (21%)
SD	3 (21%)	10 (71%)
PD	0	1 (7%)
Early death	2 (14%) [a]	0

ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LN = lymph node; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ICI = immune checkpoint inhibitor; MVAC = methotrexate, vinblastine, doxorubicin and cisplatin; RECIST = Response Evaluation Criteria in Solid Tumors.
We measured baseline in patients after progression on ICIs and before starting on subsequent line of chemotherapy. Radiological assessments were performed during chemotherapy and after a maximum of 4 wk after completion of chemotherapy.
[a] Radiological imaging was not performed due to rapid progression of the patients.

DISCUSSION

Our results show that patients who receive CT for the first time after ICIs maintain a high response rate to the CT (64%), which suggests a lack of cross resistance between the two classes of agents. The same appears to apply to patients in cohort B who have previously received both CT and ICIs. CT response rates of 21% are in line with expected results in patients who have previously failed CT without the previous ICI exposure (4). Together these results suggest that CT responses are maintained irrespective of previous exposure to ICIs in MUC. These results are too premature to support the hypothesis that synergy exists between these agents. Our results are particularly important in CT-naive patients, where the CT appears to have significant activity (2,3). Patients with progression on ICIs should, in our opinion, receive subsequent platinum-based CT to potentially maximize outcomes. The short median progression free survival on ICIs and aggressive nature of the MUC mean switching to CT in a timely manner, which is likely to be clinically important (7,8). This was highlighted by the two early deaths from cohort A in our series.

These data suggest that ICIs should not necessarily be considered as a replacement for CT, but instead both treatment modalities have a role to play in the management of

the disease. Whether or not the optimal approach is sequencing or combining these modalities together will be answered formally in prospective trials. Limitations of the study include the small sample size, its retrospective nature, and short follow-up period, which precluded further insights into the efficacy of ICIs on long-term survival and make our findings solely hypothesis generating. The lack of detail around the ICIs is also problematic, although it is needed to protect the integrity of the trials. Further ongoing randomized trials will potentially validate these findings.

Overall, sequencing CT after ICIs is likely to be important in maximizing outcomes in MUC. This appears particularly relevant in the CT-naive population where subsequent CT appears to have significant activity.

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