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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 maximise 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 maximise outcomes.

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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.

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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 maximise 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. 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 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 tumour assessments with cross-sectional imaging every 8 wk 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 favourable-, intermediate-, and poor-risk groups [8].

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].

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		
Gemcitabine/cisplatin		11 (79%)
Gemcitabine/carboplatin		1 (7%)
Paclitaxel/carboplatin		1 (7%)
MVAC		1 (7%)
Chemotherapy regimen post-ICI		
Gemcitabine/cisplatin	4 (29%)	1 (7%)
Gemcitabine/carboplatin	10 (71%)	3 (21%)
Carboplatin/paclitaxel	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.

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).

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