Clinical characteristics and outcomes for young patients with advanced urothelial carcinoma

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Introduction

Bladder cancer is the fourth most common diagnosed malignancy in North America and is predominantly a disease of the elderly.[1] The majority of bladder cancer comprises localized, non-invasive tumors; however, a small subset will go on to develop metastatic disease. Metastatic bladder cancer is an aggressive entity with median survival ranging between 12–15 months.[2] First-line systemic therapy is platinum-gemcitabine or methotrexate-vincristine-Adriamycin-platinum combination systemic therapy, with equivalent outcomes. The median age at diagnosis of bladder cancer is approximately 73; however, a small minority (<10%) are diagnosed below the age of 60.[1] Series to date on outcomes of young patients suggest that most present with non-invasive, low-grade disease and require only transurethral resection.[3] Data on outcomes of young patients with advanced disease are limited; specifically, there are no reports on how these patients fare on systemic therapy. Subgroup analysis of various clinical trials in metastatic bladder cancer have not identified age as a risk factor for survival or progression.[4] However, a small, retrospective series suggested that younger patients who go on to require cystectomy may have faster time to recurrence compared to a random sampling of elderly patients.[5] Therefore, the objective of this study was to determine the demographics and natural history of patients ≤55 years old with metastatic urothelial carcinoma who receive first-line cisplatin-based chemotherapy.

Methods

The British Columbia Cancer Agency Database was queried for patients aged ≤55 from 2000–2018 who received at least one cycle of first-line cisplatin-based systemic therapy for metastatic urothelial carcinoma. A retrospective chart review was then carried out for tumor characteristics, details of treatment, treatment response, and various laboratory parameters at diagnosis. Radiological progression was defined according to RECIST criteria,[6] and clinical progression was taken as per the treating clinician's assessment. Kaplan-Meier analysis with log-rank tests was used to compare progression and survival among different potential risk factors. Statistical analysis was carried out using SPSS software. A p-value less than 0.05 was taken as significant.

Results

Of 250 patients who received first-line cisplatin therapy for metastatic urothelial carcinoma, 66 were under age 55. The median age was 51, ranging from 35–55 years (Table 1). The majority were male (80%) and most tumors were smoking-associated (65%). Median Eastern Cooperative Oncology Group (ECOG) score was 1. All patients received cisplatin-gemcitabine, except for one who had cisplatin-methotrexate-vincristine. Approximately one-third of patients presented with de novo metastatic disease and 45% had previous cystectomy; however, only three patients (10% who received cystectomy for muscle-invasive bladder cancer [MIBC]) received perioperative chemotherapy. For patients without de novo metastatic disease, median time to metastatic disease was 11.4 months. Twenty-four percent had variant histologies, with the most common being micropapillary (n=4) and squamous (n=3). Twenty-seven patients had visceral metastases at diagnosis. Median overall survival (OS) and progression-free survival (PFS) were 10.6 and 7.1 months, respectively (Fig. 1). Thirty-seven patients had at least a partial response to first-line cisplatin. However, over 40% of patients (n=29) were unable to complete initial chemotherapy, mostly due to progression (n=16) followed by adverse events (n=13) (Fig. 1). The presence of visceral metastases was significantly associated with poorer OS and PFS (7.7 vs. 13.7 months; 4.5 vs. 8.9 months; p<0.05) (Table 2). There was a trend towards worse OS in patients with ECOG ≥2 (5.2 vs. 13.3 months, p=0.06). Of the laboratory param-

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Table 1. Patient and tumor characteristics (n=66)

Characteristic	Number (%)
Male gender (%)	53 (80%)
Median age (years)	51 years (range 35–55)
Smoking-associated	64 (68%)
Variant histology	16 (17%)
Visceral metastases	27 (41%)
ECOG	
0	21
1	29
2	11
≥3	5
Best response to systemic therapy	
Complete response	8
Partial response	29
Stable disease	6
Progression	22
De novo metastatic disease	24 (36%)
Previous cystectomy	30 (45%)
Neoadjuvant or adjuvant chemotherapy for MIBC	3 (10%)
Deceased at last followup	58 (88%)

ECOG: Eastern Cooperative Oncology Group; MIBC: muscle-invasive bladder cancer.

eters examined, anemia (8.7 vs. 14.8 months, p=0.09) and hypoalbuminemia (5.7 vs. 12.9 months, p=0.262) trended towards poorer OS, but were significantly associated with worse PFS.

Twenty-four patients went on to receive salvage chemotherapy after progression (Table 3). This comprised mostly taxane-based regimens (n=14), platinum re-challenge (n=6), and immunotherapy or clinical trial (n=4). Patients who received salvage therapy had improved median OS (17.3 vs. 8.5 months, p<0.05). Median PFS for salvage therapy was 3.4 months for all regimens.

Discussion

This is one of the first studies to report on the outcomes of young patients with metastatic bladder cancer. Our results suggest that younger patients may have worse outcomes compared to the overall disease population. Data from previous clinical trials, as well as large database series report a median OS ranging from 14–16 months with first-line platinum-based chemotherapy. In contrast, the median OS for our cohort was only 10.6 months, despite being 10 years younger than patients in the Van der Maase trial.[2] On the other end, Surveillance, Epidemiology, and End Results (SEER) data looking at elderly patients (≥66 years) reveals an OS of 12 months.[7] Indeed, one would expect outcomes for younger patients to be at least equivalent to the overall metastatic bladder cancer population, given improved performance status, decreased comorbidities, and perhaps improved tolerance of systemic therapy. Despite this, most patients in our cohort were unable to complete first-line platinum therapy and had poorer outcomes than other studies looking at very elderly patients.

This far, data on young patients with bladder cancer is limited to small, retrospective series that include mostly patients with non-muscle-invasive disease. A review of the National Cancer Database comparing young (<40) to older patients with bladder cancer reported that younger patients were more likely to harbor less invasive disease and accordingly had improved OS.[8] However, younger patients who required cystectomy were more likely to have nodal and distant metastases. In line with this, Yossepowitch et al[5] report poorer recurrence-free survival in patients under 40 years old who require cystectomy. These findings, along with our results, suggest there may be two distinct populations of young patients with bladder cancer: 1) the majority with indolent non-muscle-invasive disease; and 2) a smaller subset with more aggressive features that carry poorer outcomes compared to older patients of similar stage.

A

First-line treatment	Number
Cisplatin-Gemcitabine	65
Methotrexate-Vincristine-Cisplatin	1
Unable to complete planned therapy	29
Progression	16
Adverse events	11

B

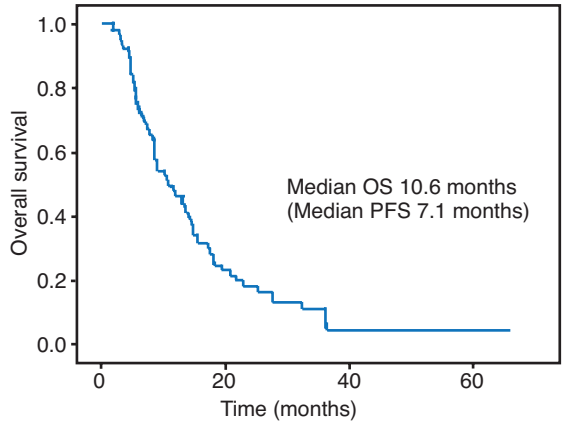

Fig. 1. (A). Study results. ***(B)*** Median overall survival (OS) and progression-free survival (PFS).

Table 2. Factors associated with survival and progression for young patients with metastatic bladder cancer

Subgroup	Median overall survival (months)		Median progression-free survival (months)	
Hemoglobin				
<100	8.7		6.0*	
>100	14.8	p=0.094	9.4	p=0.040
Visceral metastases				
Yes	7.7 *		4.5*	
No	13.7	p=0.016	8.9	p=0.026
Albumin				
<30	5.7		3.8*	
>30	12.9	p=0.262	8.2	p=0.032
De novo metastatic disease				
Yes	10.4		7.8	
No	13.0	p=0.063	7.1	p=0.806
ECOG >2				
Yes	5.2		2.8	
No	13.3	p=0.055	8.2	p=0.076
Use of salvage systemic therapy				
Yes	17.3			–
No	8.4	p<0.0001		–

*p<0.05 by log-rank test. ECOG: Eastern Cooperative Oncology Group.

A potential mechanism behind these worse outcomes remains unknown. From a basic oncological perspective, our group of younger patients seem similar to that expected in the general disease population. The cases captured in our study appear to be mostly smoking-associated, and only two cases were related to other exposures (previous radiation and indwelling catheter). The prevalence of variant histology was also consistent with that seen in the overall population. The youngest patient we identified was 35, and most were over 50 years of age. Overall, this is concordant with urothelial carcinoma in younger patients still being a result of repeated carcinogen exposure as opposed to sporadic or genetic.

Seiler et al[9] examined mutational burden and transcriptomic profiles of patients over and under 50 years of age with muscle-invasive bladder cancer. They report that those <50 years had lower mutational burden and less immunogenic tumors. If these findings are extended to the metastatic setting, decreased mutational burden may negatively impact susceptibility to cisplatin, and lower cytokine expression could translate into diminished anti-tumor immune activity in younger patients. The response rate to platinum in our cohort was similar to that of large clinical trials;[2] however, it was mostly not durable. The finding from Seiler et al's study that would be difficult to extrapolate to our population is that younger patients were more likely to have luminal subtype tumors, which are associated with improved prognosis. However, tumors likely undergo further genomic alteration at metastatic transformation, and whether younger patients may harbor more potent driver mutations remains unknown.

Table 3. Outcomes of salvage chemotherapy in young patients with metastatic urothelial carcinoma

Regimen	Number	Median progression-free survival (months)
Platinum-gemcitabine re-challenge	6	6.8
Taxane monotherapy	13	1.8
Taxane/platinum combination	1	6.7
Clinical trial	3	4.5
Atezolizumab	1	3.1
Total	24	3.4

The impact of age has been looked at in more detail in metastatic colorectal[10] and lung cancers.[11] These patients tend to present with more advanced disease; however, survival seems unchanged or improved. Younger patients also have different mutation profiles, including a greater proportion of driver mutations in lung cancer (epidermal growth factor receptor [EGFR]).[11,12] From a psychosocial perspective, younger patients may be less likely to present earlier at the onset of symptoms. Whether these patterns apply to urothelial carcinoma remains unknown.

Visceral metastases, anemia, hypoalbuminemia, and poor performance status were previously established as adverse prognostic predictors using a cohort of patients in phase 2 clinical trials (Bajorin risk factors).[4] We identified visceral metastases as a risk factor for decreased survival in young patients with metastatic bladder cancer on cisplatin-based therapy. The other Bajorin factors were strongly associated with poorer OS and were often very close to reaching statistical significance. Low albumin and anemia were significantly associated with poorer PFS. Patients who received salvage systemic therapy had improved survival; however, this likely represents a selection bias of those fit enough to be challenged with second-line treatments.

The largest limitation of our data is that we have not included a direct comparison cohort with patients greater than 55 years. However, the outcomes of this group are well-defined through clinical trials and larger databases such as SEER.[7] Furthermore, our survival estimates may be overestimates for young patients because we excluded those who did not receive cisplatin-based chemotherapy (including carboplatin). While most studies used 40 or 50 as their age cutoff, these were not specifically looking at metastatic disease, and we felt additional time would be required for patients to progress to progress to metastatic disease. Furthermore, based on SEER data[1] for incidence of bladder cancer, age 55 would still encompass the youngest 10% of all patients.

Conclusions

Metastatic urothelial carcinoma in young patients appears to be an aggressive entity with poor survival, at least comparable to elderly patients. Many are unable to complete systemic therapy and decline rapidly after first progression. Known risk factors for survival were also validated in this unique cohort. Larger, confirmatory studies and better treatments for this population are needed.

Competing interests: Dr. Black has attended advisory boards for AbbVie, Amgen, Astellas, Biocancell, Cubist, Janssen, Novartis, and Sitka; has been a speaker for AbbVie, Janssen, Ferring, Novartis, and Red Leaf Medical; has received grants/honoraria from Pendopharm; has participated in clinical trials supported by Amgen, Astellas, Ferring, Janssen, and Roche; and has received research funding from GenomeDx, iProgen, Lilly, and New B Innovation. Dr. Eigl has received honoraria and travel support from Astellas, AstraZeneca, Bayer, Janssen, Merck, and Roche. The remaining authors report no competing person or financial interests related to this work.

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