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Management Practices of Locally Advanced and Metastatic Urothelial Carcinoma: A Questionnaire-Based Survey among Lebanese Oncologists

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Abstract

Background and Objective: The outcome of locally advanced and metastatic urothelial carcinoma LA/mUC has improved over the past years with a plethora of new treatments and the approval of immune checkpoint inhibitors (ICIs), antibody-drug conjugates, and targeted agents, to identify locally advanced metastatic urothelial carcinoma's current management practices in Lebanon and the implication of the ongoing economic crisis on the medical practice. **Methods:** An online questionnaire was used to survey ten Lebanese oncologists from six different hospitals, between July 5 and July 11, 2022, requesting information pertaining to their current clinical practice in the pharmacological treatment of locally advanced metastatic urothelial carcinoma. **Key Findings:** Cisplatin-based chemotherapy was the most frequently reported initial treatment of locally advanced metastatic urothelial carcinoma. Participants reported using immune checkpoint inhibitors in platinum-ineligible patients and those with PDL1 positive tumors. Also, they

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would not consider the concomitant use of immunotherapy and chemotherapy in the first-line setting. Participants believed that avelumab maintenance is effective in the absence of progression after first-line platinum-based chemotherapy; they would consider initiating it 2 - 10 weeks after completion of chemotherapy. **Conclusions and Clinical Implications:** After comparing with current international guidelines, this study shows that Lebanese oncologists follow international guidelines and have deep knowledge of recent clinical trials for the management of locally advanced metastatic urothelial carcinoma, regardless of economic crisis challenges.

Keywords

Clinical Practice, Chemotherapy, Immune Checkpoint Inhibitors, PDL1, Urothelial Carcinoma

1. Introduction

According to estimates from Global Cancer Statistics, approximately 573,000 new bladder cancer (BC) cases were diagnosed in 2020, accounting for 3% of all new cancer cases worldwide [1]. In addition, there were 213,000 deaths due to BC, constituting around 2% of the total cancer deaths in 2020 [1]. BC incidence and mortality were three to four times higher in men, with age-standardized incidence and mortality rates of 9.5 and 3.3 per 100,000, respectively [1]. This incidence discrepancy between the genders is reflected by the difference in the prevalence of tobacco smoking, which is considered the most common risk factor for BC. Other risk factors include occupational and environmental exposures to toxic chemicals and schistosomiasis infection in some regions of the world, such as Africa and the Middle East [2]. In 2019, Lebanon was among the 3 countries with the highest BC incidence worldwide, with an age-standardized incidence rate estimated at 30.2 (23 to 40.4) per 100,000. Among all countries, Lebanon had also the highest age-standardized death rate due to BC (10.4 [8.1 to 13.7] per 100,000) [3].

Urothelial carcinoma (UC) is the most common histologic type of BC. While 75% of BCs are classified as non-muscle invasive, about 25% are muscle-invasive, and 5% are metastatic at presentation. Among patients with muscle-invasive BC, around 50% will develop metastatic disease [4]. Cisplatin-based combination chemotherapy is the standard of care first-line treatment for patients with locally advanced and metastatic urothelial carcinoma (LA/mUC) who are platinum eligible [5]. The median overall survival (OS) with cisplatin-based chemotherapy is approximately 15 months [6] [7], compared to the 6-months for untreated LA/mUC.

Recently, the treatment landscape of LA/mUC has significantly expanded, as there has been substantial improvement in survival with the advent of immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADC), and targeted agents.

In Lebanon, the recommendations developed by the Ministry of Public Health (MoPH) in 2018 [8] do not include some of the current treatment options approved by international guidelines based on findings of recent clinical trials. To our knowledge, no report exists regarding the clinical practices followed for the treatment of LA/mUC in Lebanon, and the data from the National Cancer Registry in Lebanon are either out of date or do not necessarily include the treatment that was provided for LA/mUC. The objective of this study was to describe the current therapeutic landscape of LA/mUC in Lebanon. The aim was to gain insights into future perspectives for the management of LA/mUC in Lebanon, in light of recent treatment advances on one hand and the current Lebanese economic crisis, affecting treatment availability, on the other hand, as well as to promote and facilitate the update of the Lebanese recommendations for the treatment of LA/mUC.

2. Methods

This study used a questionnaire-based survey to elicit information from medical oncologists on their current practices for treating LA/mUC in Lebanon. It included 10 oncologists who practiced in 6 different Lebanese hospitals and constituted the 2022 Lebanon Genitourinary Cancer OncoBoard. The Lebanese key experts' oncologists were selected based on their clinical familiarity, patients' load, and knowledge about LA/mUC, working in university hospitals, 5 of which are located in Beirut, the capital and the largest most populous city of Lebanon and 1 located in Baabda (The university hospitals are Hotel-Dieu de France Saint-Joseph University hospital, American University of Beirut Medical Center, Saint Charles Hospital, Makassed General Hospital, Lebanese American University Medical Center - Rizk Hospital, Saint George Hospital University Medical Center). According to the survey, around 184 locally advanced/metastatic UC patients are treated by these oncologists.

They were invited by email to complete an online survey of 31 questions (supplementary doc. 1) between July 5th and July 11th, 2022. Reminders were sent by email to ensure that all oncologists have completed the questionnaire by July 11th, 2022.

The questions focused on the epidemiology of LA/mUC in the oncologists' clinical practices, the patients clinical baseline characteristics influencing their treatment decisions, their general management of LA/mUC, and their knowledge about the treatment landscape of LA/mUC.

All aspects of this OncoBoard, including the input disclosed, remained confidential. All oncologists' names and organizations were kept anonymous in the analyses and final report. As the study did not directly involve any patients, ethics committee approval and informed consent were not sought.

3. Results

3.1. Epidemiology of LA/mUC in the Oncologists' Clinical Practices

Over the past 12 months, each oncologist personally managed an average of 18

patients with LA/mUC (min: 4; max: 50). In their clinical practices, the percentage of men with LA/mUC was 70% versus 30% in women. The mean age of LA/mUC patients at diagnosis was 66.9 years old (min: 64; max: 70). Overall, 40% of UC patients who were metastatic at diagnosis (min: 10%; max: 80%) while 57% progressed to advanced disease (min: 15%; max: 90%), according to the clinical practice of the 10 oncologists.

The main reported risk factors associated with bladder cancer were smoking (cigarettes and waterpipe), age, and male gender. Other risk factors included air pollution and exposure to toxic chemicals/industrial products, such as painting materials and benzene.

3.2. General Treatment Landscape in LA/mUC

In this survey, oncologists confirmed that they follow the European Society for Medical Oncology (ESMO) [5] and the National Comprehensive Cancer Network (NCCN) [9] [10] guidelines, in addition to the recommendations of the Lebanese MoPH. One oncologist reported using the guidelines of the European Association of Urology [11]. They admitted deviating occasionally from the guidelines in certain circumstances related to patient status, drug availability, and approval of guarantors.

Table 1 presents the regimen and treatment sequence most often used by the Lebanese oncologists in the treatment of LA/mUC patients. Oncologists in this study preferred cisplatin-based chemotherapy as the first-line treatment of LA/mUC. In patients considered cisplatin-ineligible, or those with programmed death-ligand 1 (PD-L1) positive tumors, oncologists would consider using carboplatin-based regimens or ICIs, such as pembrolizumab or atezolizumab. Oncologists would also use front-line ICIs in platinum-ineligible patients, regardless of PD-L1 status. Besides ICIs, vinflunine was considered by 3 oncologists in the second-line setting. Enfortumab vedotin (EV, a monoclonal antibody-drug conjugate) and erdafitinib (an anti-fibroblast growth factor receptor, FGFR) were considered by 2 and 4 oncologists, respectively, in the platinum and immunotherapy refractory settings, subject to availability.

3.3. Clinical Baseline Characteristics of LA/mUC Patients, Influencing Treatment Decisions

Table 2 lists the clinical baseline characteristics of LA/mUC patients, influencing the oncologists' treatment decisions, assuming all treatment options are available in Lebanon, independently of the cost impact. The average percentage of platinum-ineligible LA/mUC patients reported by the oncologists in their practices was 33% (min: 10%; max: 60%). The following criteria were considered to identify platinum ineligible patients: Eastern Cooperative Oncology Group (ECOG) performance status of 2 or more, creatinine clearance (CrCl) < 50 - 60 ml/minute, New York Heart Association (NYHA) Class III heart failure, neurotoxicity (Criteria for adverse events (CTCAE) version 4.0 grade ≥ 2 neuropathy),

Table 1. Treatment sequence most often used in locally advanced/metastatic UC patients by the Lebanese oncologists included in the survey.

Oncologist	Line			
	First	Second	Third	Subsequent line
1	- Gemcitabine plus platinum-based regimen followed by avelumab if platinum-sensitive - PD1/PD-L1 inhibitors (pembrolizumab or atezolizumab) if platinum ineligible	- PD1/PD-L1 inhibitors if not received in first line - Vinflunine - Anti-FGFR2/3	- Chemotherapy	
2	- Gemcitabine plus cisplatin or dd-MVAC for cisplatin-eligible - Gemcitabine plus carboplatin for cisplatin-ineligible	- PD1/PD-L1 inhibitors	- Vinflunine	- EV - Erdafitinib (FGFR3 or 2 alteration) not available in Lebanon
3	- Platinum-based chemotherapy - PD1/PD-L1 inhibitors for platinum ineligible	- PD1/PD-L1 inhibitors if not received in first line	- BSC	- BSC
4	- Gemcitabine plus platinum-based regimen	- PD1/PD-L1 inhibitors	- Taxane-based chemotherapy	- MVAC regimen
5	- Gemcitabine plus platinum-based regimen	- PD1/PD-L1 inhibitors (pembrolizumab, nivolumab, avelumab)	- Vinflunine	- EV
6	- Gemcitabine plus platinum-based regimen or dd-MVAC	- PD1/PD-L1 inhibitors	- Single agent chemotherapy (Taxane)	- Non-platinum combination
7	- Cisplatin-based chemotherapy for cisplatin-eligible patients, followed by avelumab maintenance. - Carboplatin plus gemcitabine for cisplatin-ineligible patients, followed by avelumab maintenance. - Alternatively, if CPS is more than 10% in the cisplatin-ineligible population, first-line pembrolizumab can be considered.	- PD1/PD-L1 inhibitors (pembrolizumab or nivolumab) if the patient did not receive maintenance avelumab - Vinflunine or preferably EV if maintenance avelumab was given, and if available in Lebanon.	- Vinflunine or taxane or FGFR3 inhibitors if they have a mutation by NGS (erdafitinib is not available in Lebanon)	
8	- Gemcitabine plus carboplatin or cisplatin	- Vinflunine or PD1/PD-L1 inhibitors	- Vinflunine or PD1/PD-L1 inhibitors	- Taxane weekly or anti-FGFR3 if available
9	- Gemcitabine plus cisplatin	- PD1/PD-L1 inhibitors (Pembrolizumab or nivolumab)	- Taxane	- BSC

Continued

10	- Gemcitabine plus cisplatin - Gemcitabine plus carboplatin (less frequently) - Atezolizumab or pembrolizumab (rarely)	- Pembrolizumab	- Vinflunine	- Taxane

Abbreviations: BSC, Best supportive care; CPS, combined positive score; dd-MVAC, Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EV, Enfortumab Vedotin; FGFR, Fibroblast growth factor receptor; NGS Next-generation sequencing; PD1/PD-L1, Programmed death-1/Programmed Cell Death Ligand 1.

and/or CTCAE version 4.0 grade ≥ 2 audiometric hearing loss.

As for the availability of ICIs in Lebanon, the oncologists stated that pembrolizumab, nivolumab and atezolizumab were available only intermittently in Lebanon due to the current financial situation in the country.

None of the oncologists considered the concomitant use of immunotherapy and chemotherapy in the first-line setting, except in the context of a clinical trial. Instead, they would opt for chemotherapy followed by avelumab maintenance provided there was no progression after chemotherapy. The oncologists reported that they would consider avelumab maintenance in the following instances: 1) in patients without disease progression after first-line chemotherapy; 2) in patients with poor prognostic factors (depending on renal function, hepatic and hematologic status, and performance status); 3) in case of drug availability and third-party approval. Some oncologists deemed that all patients, except those unfit for chemotherapy, may benefit from avelumab maintenance, independently of PD-L1 status. Regarding the number of platinum-containing chemotherapy cycles to be given before starting avelumab maintenance, the oncologists considered 4 cycles to be reasonable for unfit patients while they would give up to 6 cycles to fit patients, or if avelumab was not available, or in the case of high initial tumor burden.

Most participant oncologists would not consider exchanging ICIs during maintenance, as there is no data available on switching between ICIs, and avelumab is currently the only approved ICI in the maintenance setting.

3.4. Discussion

The present survey revealed that Lebanese oncologists, represented by the participant oncologists, generally managed LA/mUC patients in accordance with international guidelines, including ESMO [5] and NCCN [9] [10] and they are aware of the findings from latest published and recent clinical trials. As per the 2022 ESMO and NCCN guidelines, cisplatin-based chemotherapy remains the preferred first-line therapy for LA/mUC, given high response rates up to 72% and a median OS of 14 - 15 months [6] [7]. However, resistance to chemotherapy results in short response durations and high rates of disease recurrence. In patients not eligible for cisplatin, carboplatin-based chemotherapy is considered an alternative first-line treatment option, despite its lower response rates and

Table 2. Clinical baseline characteristics of locally advanced/metastatic UC patients influencing treatment decisions of the Lebanese oncologists included in the survey.

Treatment option	Clinical baseline characteristics
Combination chemotherapy (cisplatin-based chemotherapy/gemcitabine + carboplatin)	• For cisplatin-based chemotherapy, the patient has to have: ○ A good ECOG performance status ○ Good renal function (creatinine clearance: >60 mL/minute) ○ Good cardiac function • For carboplatin-based chemotherapy, the experts often give it to patients with poor performance status, renal failure so as to adjust according to GFR as well as those with compromised cardiac function. • Other factors to consider are age, hematologic and hepatic functions, neuropathy, and hearing status.
Pembrolizumab	• ECOG performance status • Unfit patient • Renal function impairment • Cardiac failure • MSI-H tumors • PD-L1 positivity in first line • Platinum ineligibility • Autoimmune conditions • In all patients in second line if not used in first line for advanced setting or after failure of first-line platinum-based chemotherapy • In the first-line setting in patients who are cisplatin-ineligible
Atezolizumab	• ECOG performance status • Unfit patient • Renal function impairment • Cardiac failure • PD-L1 status in first line • PD-L1 positivity in first line • Platinum ineligibility • Autoimmune conditions • In all patients in second line if not used in first line for advanced setting • In the first-line setting in patients who are cisplatin-ineligible
Nivolumab	• ECOG performance status • Platinum ineligibility • Autoimmune conditions • In the adjuvant patient in patients who received or not neoadjuvant chemotherapy; all comers can benefit from this treatment • In the second-line setting after failure of first-line chemotherapy regimen whether cisplatin or carboplatin Not recommended as first-line option but in subsequent lines in case of resistance to platinum. One expert reported not using nivolumab for the treatment of locally advanced/metastatic UC patients.
The FGFR inhibitor erdafitinib	• In second- or third-line patients harboring FGFR2 and 3 genetic alterations • Creatinine clearance • Resistance to first-line platinum with NGS that showed expression of FGFR or amplification

Continued

Avelumab in maintenance	• In patients who received chemotherapy platinum-based chemotherapy for advanced setting provided they have no underlying autoimmune disease that precludes the use of immune checkpoint inhibitors • Objective response or stable disease following first-line platinum-based therapy • Response to the Javelin 100 chemotherapy scheme • Autoimmune conditions • Platinum ineligibility

ECOG, Eastern Cooperative Oncology Group; FGFR, Fibroblast growth factor receptor; GFR, Glomerular filtration rate; MSI-H, High microsatellite instability; NGS, Next-generation sequencing; PD-L1, Programmed Cell Death Ligand 1.

shorter median OS (9 months) [12]. As reported by Lebanese oncologists, determining the eligibility for cisplatin is crucial for the choice of first-line therapy. For cisplatin ineligible and whose tumors express PD-L1 and for platinum ineligible patients regardless of PD-L1 status, ICIs are recommended in first-line: atezolizumab (anti-PD-L1) or pembrolizumab (anti-PD-1), based on the results of the phase 2 studies, IMvigor 210 [13] and Keynote-052 [14] [15], demonstrating a median OS of 16 months and 11 months and long-term responses (70% responses ongoing at 17.2 months and 39.4% responses ongoing at ≥48 months) for atezolizumab [13] and pembrolizumab [14] [15], respectively.

In the present survey, oncologists responded that they do not prescribe chemotherapy concomitantly with immunotherapy as first-line treatment for LA/mUC patients, as there is no evidence yet of a synergistic effect for this combination in this setting [16] [17].

Responses from our survey revealed that most oncologists treat patients with disease progression during or after platinum-based chemotherapy with PD1/PD-L1 inhibitors. Indeed, five different ICIs have been found to be effective as second-line treatment after chemotherapy failure. However, pembrolizumab is the only ICI with full FDA approval for this indication, based on the results of the phase 3 Keynote 045 study [18]. Pembrolizumab in the second line setting was associated with a significantly longer median OS (10.1 versus 7.3 months, HR 0.70, 95% CI 0.57 - 0.85) compared to chemotherapy. The choice of ICIs among Lebanese oncologists is mainly driven by the availability of these agents in Lebanon due to the financial situation in the country.

In the present survey, chemotherapy with vinflunine and taxanes was considered by 90% of the oncologists in later treatment lines after platinum-based chemotherapy. Vinflunine has been approved as a second-line treatment only in Europe, based on the results of a phase 3 study comparing vinflunine to best supportive care. In this trial, vinflunine showed improved response rate with no statistical survival benefit [19]. Paclitaxel is also considered a viable second-line treatment option after platinum-based regimens, in settings where there is no access to novel therapies, since paclitaxel has a RR of around 25% [20].

Other options considered by Lebanese oncologists include erdafitinib and EV, depending on their availability. A phase 2 trial of erdafitinib in 87 LA/mUC pa-

tients with FGFR alterations whose disease had progressed during or after chemotherapy showed a response rate of 32.2%, and a median response duration of 5.4 months [21]. Based on these results, erdafitinib was approved in patients with FGFR3 or FGFR2 genetic alterations whose disease had progressed during or after platinum-based chemotherapy. FDA approved EV based on a phase 2 trial showing a response rate of 44%, a median PFS of 5.8 months, and a median OS of 11.7 months [22]. A subsequent randomized trial of EV in patients with LA/mUC whose disease had progressed after platinum-based chemotherapy and ICIs [23], demonstrated significantly improved overall survival compared to standard chemotherapy.

In this survey, oncologists considered the use of avelumab in the setting of an objective response or stable disease after first-line platinum-based therapy. This is based on the results and clinical implications of the Javelin Bladder 100 trial [24], which reported a significantly longer overall survival with avelumab maintenance compared to best supportive care alone in patients who had not experienced disease progression after first-line platinum-based chemotherapy. Consequently, avelumab is now recommended as first-line maintenance therapy in different guidelines [5] [9]. A subsequent exploratory analysis evaluated the role of various biomarkers of tumor homeostasis and chronic inflammation, including PD-L1 protein expression, in predicting improved survival with avelumab maintenance therapy [25]. Participant oncologists were aware that this improvement in survival was independent of all the tested biomarkers. They reported that they would opt for 4 to 6 cycles of platinum-based chemotherapy, depending on treatment tolerance, clinical and radiological responses, age, and comorbidities.

The Lebanese economic crisis, which has been ongoing since 2019, has had a profound impact on various sectors of the country's economy, including healthcare. It is primarily attributed to persistent political corruption, leading to the devaluation of the local currency in 2020. The depreciation of the Lebanese pound caused the central national bank to collapse, subsequently destabilizing the healthcare system [26]. This has resulted in drug shortages, including those for cancer treatments provided by the MOPH, such as targeted and hormonal therapies. The crisis has caused major disruptions in the pharmaceutical industry, making it increasingly difficult for patients to access lifesaving medications [27]. Despite the ongoing economic crisis, it is imperative that the practice of oncology and continuous medical education continue to progress. Keeping up to date with the latest advancements in oncology is essential in providing effective treatment and improving patient outcomes. Furthermore, continuous medical education helps to ensure that healthcare professionals remain knowledgeable which is crucial to maintain high standards of medical practice, regardless of the economic challenges they may face.

Several limitations to the current study involve the nature of survey research and the small sample of oncologists included in the study. Very common disadvantages of surveys are related to respondents not providing accurate and honest

answers or may feel uncomfortable presenting themselves in an unfavorable manner. Moreover, although coming from 6 different treatment centers in Lebanon, this population may not per say represent the whole population of oncologists and all the medical centers in Lebanon.

4. Conclusion

This survey revealed that most Lebanese oncologists follow international guidelines for the management of LA/mUC. However, their therapeutic strategies are influenced by drug availability, economic crisis, drug shortage, and patient status. The Lebanese guidelines for the management of LA/mUC should consider the recent changes in this cancer's treatment landscape and adapt the international clinical guidelines to the local context.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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