Updates on management of metastatic bladder cancer

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SUMMARY: Metastatic urothelial cancer is the 13th most common cancer in Ireland and has a 5 year survival rate of 5%. First line treatment with platinum based chemotherapy has been shown to give objective responses with a median overall survival (OS) of 12 months, but traditionally does not result in maintained response. Immunotherapy and targeted therapies have been increasingly shown to improve outcome in the second line setting and beyond. We discuss the updated management of metastatic urothelial cancer in this article.

Date	Clinical Trial	Type of Immunotherapy	Primary endpoint	Outcome
16 Mar 2017	Phase III KEYNOTE-045 Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma[12]	Pembrolizumab	OS	Pembrolizumab vs chemo: 10.3 months vs 7.4 months (HR 0.73; 95% CI, 0.59 to 0.91; P=0.002)
25 Jan 2017	Phase II CHECKMATE 275 Nivolumab in metastatic urothelial carcinoma after platinum therapy[13]	Nivolumab	Objective response rate (ORR)	Single arm Nivo: 20.4 ORR Median OS 8.6 months
17 Sept 2017	Phase II Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma[14]	Durvalumab	ORR	Single arm durvalumab: 17.8 ORR Median OS 18.2 months
5 Dec 2017	Phase 1 Avelumab in Metastatic Urothelial Carcinoma After Platinum Failure (JAVELIN Solid Tumor): Pooled Results From Two Expansion Cohorts of an Open-Label, Phase 1 Trial[15]	Avelumab	ORR	Single arm avelumab: 16.1 ORR

Table 1

In Europe, the annual incidence rate of bladder cancer is 20.4/100 000 with an estimated 151 297 new cases per year. In the Irish context, the national cancer registry of Ireland in 2015 shows an incidence rate of 17.4/100000 with a male preponderance of a ratio to 2:1. It is the 13th most common cancer in Ireland and approximately 70% of patients diagnosed with bladder cancer are >65 years of age. Up to 15% are diagnosed with metastatic disease at initial presentation.1

The most common presenting symptom seen in >80% of patients is painless haematuria. Other symptoms include dysuria, frequency or urgency, and rarely bone or flank pain due to metastases. The top risk factors for bladder cancer include tobacco smoking, radiation and occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons.

Approximately 90% of bladder cancers are urothelial (transitional cell) carcinomas. The remaining subsets are relatively rare, and these include squamous cell carcinoma, adenocarcinoma, small cell carcinoma and sarcomatoid carcinomas.2 In the following discussion we will focus on the updates on systemic therapy for metastatic urothelial cancer.

A number of clinical characteristics are correlated with shortened survival. In the first line setting, a poor performance status (PS) and the presence of visceral metastases were poor prognostic factors. Median OS times for patients who had zero, one, or two risk factors were 33, 13.4, and 9.3 months respectively (P = 0.0001)3. This survival is even shorter in the second line setting, where prognostic factors of a haemoglobin <10 g/dL, liver metastases and a poor PS conferred shortened survival.

With the presence of zero, one, two, or three prognostic factors; the median OS times for these groups were 14.2, 7.3, 3.8, and 1.7 months respectively (P < 0.001)4 Thus, it is important to take these prognostic factors into consideration when assessing whether a patient is suitable for systemic treatment.

Standard first line treatment for metastatic urothelial cancer can either be Gemcitabine/Cisplatin (GC) or MVAC (methotrexate, vinblastine, adriamycin and cisplatin). OS was similar at 13.8 months with GC and 14.8 months with MVAC (p=0.75), however GC was better tolerated and had a better safety profile.6

About 50% of patients are unfit for cisplatin-containing chemotherapy due to poor hearing, impaired renal function or comorbidity. Patients who are unable to receive cisplatin may be offered palliative chemo in the form of Carboplatin/Gemcitabine. Carboplatin/Gemcitabine is the preferred option as it is better tolerated compared to Methotrexate/carboplatin/vinblastine (MCAVI), but without a statistically significant difference in OS and progression free survival (PFS).7

Patients unfit for platinum based therapy have the option of single agent taxane or gemcitabine. Trials have shown some activity, but responses are generally of short duration from 3-9 months, and no consistent improvement in survival has been demonstrated.(8-11) Although a significant number of patients have an objective response to first-line therapy, most eventually progress and

would require subsequent lines of therapy. Options for treatment in the second line setting and beyond include immunotherapy, targeted treatment or chemotherapy.

Immunotherapy has been approved by the FDA in the second line setting for patients with metastatic urothelial cancer who progressed on previous platinum chemotherapy. Table 1 shows recent positive trials involving immunotherapy.

The phase III KEYNOTE-045 trial looked at pembrolizumab in the second line setting versus (vs) chemotherapy of physicians choice (paclitaxel, docetaxel, or vinflunine), and the median OS was 10.3 months in the pembrolizumab group compared with 7.4 months in the chemotherapy group. Improved OS was seen particularly in the patient group with a PDL-1 CPS score of ≥10%12. A recent 3 year follow up update in Sept 2019 shows a maintained improvement in median OS with pembrolizumab vs chemo (median 10.1 vs 7.2 months; HR 0.72; P = 0.0003)16

Atezolizumab initially received accelerated approval from the FDA on the basis of promising phase I and II studies. However the phase III IMvigor211 found that although duration of response was longer in the atezolizumab group than in the chemotherapy group (median 15.9 vs 8.3 months; HR 0.57), there was no significant difference in OS (median 11.1 vs 10.6 months; HR 0.87; p=0.41)17

There was a recent update in ASCO 2020 about the interim analysis of the Javelin 100 phase III trial. This looked at maintenance avelumab vs best supportive care after 1st line platinum based chemotherapy. It met it's primary endpoint of overall survival with a median overall survival of 21.4 months in the avelumab arm vs 14.3 months in the supportive care arm.18 This may represent a new standard of care for patients with advanced urothelial cancer.

Although response rates are relatively low (15% to 24%) to immunotherapy, responders can experience durable disease control. PD-L1 expression assessed by immunohistochemistry (IHC) is not a robust predictive biomarker of response and additional clinical biomarkers that can predict response are needed. Teo et al investigated DNA damage response and repair (DDR) genes, and found that patients with DDR gene alterations are more likely to have improved ORR and OS. Trials are ongoing in validating the possibility of DDR alterations being a useful predictive marker.19

For patients who relapse following treatment with a platinum-based regimen and immunotherapy, a subset may be suitable for targeted therapy. Up to 20% of patients with metastatic urothelial cancer will have a FGFR mutation. These patients have the option of targeted therapy with erdafitinib which is a potent tyrosine kinase inhibitor of FGFR1–4. A phase II clinical trial looking at erdafinib in FGFR mutated patients with advanced urothelial cancer met it's primary endpoint of a 40% response rate with a median PFS of 5.5 months and the median OS of 13.8 months. In this trial the majority of patients had at least one line of previous chemotherapy or immunotherapy.20 Currently there is a phase III clinical trial ongoing that will be exploring the benefit of erdafinib vs chemotherapy or immunotherapy.21

Enfortumab vedotin is an antibody-drug conjugate that targets Nectin-4 which has been licensed by the FDA as a 3rd line option. This was on the basis of a single arm phase 2 trial that showed an ORR of 44% and a median duration of response of 7.6 months.22 However, there is a need for randomized studies comparing enfortumab vedotin with chemotherapy and/or immunotherapy in the second or third line setting in order to prove a survival benefit. There are currently no direct comparison trials with erdafinib and enfortumab vedotin in patients with FGFR mutations.

In the Irish setting chemotherapy is the only funded treatment at the moment. Patients may be able to access immunotherapy or erdafinib via compassionate access schemes, however these applications require time and are subject to approval from the pharmaceutical companies. Thus, treatment options for patients who progress on chemotherapy are limited and do not follow recommended standards of care. With ongoing clinical trials increasingly showing an overall survival benefit with immunotherapy and targeted treatment, it will be important for us to aim to acquire access to these drugs in order to provide the best possible care for our patients. Furthermore, Irish patients will be soon overlooked for future trials if our standard of care does not keep pace with evolving practice.

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