Bladder cancer is the tenth most common cancer in the UK, yet the seventh most common cause of cancer death. There were 10,063 new cases of bladder cancer diagnosed in the UK in 2014, with 5,369 deaths from the disease.\(^1\) For the majority of patients, the disease remains indolent following initial treatment of superficial tumours, whereas those with muscle-invasive bladder cancers have a poor prognosis despite intensive treatment (Figure 1).\(^2\) For many years, platinum-based combination chemotherapy has been the mainstay of treatment in this group, with median overall survival of around 12–14 months and limited second-line treatment options.\(^3\) More recently, however, there have been exciting advances, particularly with immunotherapy, that promise to improve the outlook for patients with metastatic bladder cancer.

**FIRST-LINE CHEMOTHERAPY IN INOPERABLE AND METASTATIC BLADDER CANCER**

Since 1985, when Sternberg et al. demonstrated that transitional cell carcinomas (TCC) of the urothelial tract
were sensitive to chemotherapy, first-line treatment of metastatic urothelial bladder cancer has revolved around cisplatin-based chemotherapy regimens. Initial studies used the MVAC regimen (methotrexate, vinblastine, doxorubicin and cisplatin), which while demonstrating efficacy against the disease, also showed significant toxicity. In their cohort, 4% of patients had a drug-related death, 20% neutropenic sepsis and 31% renal toxicity. A subsequent randomised study comparing gemcitabine and cisplatin (GC) with MVAC in advanced bladder cancer demonstrated comparable efficacy, with a median survival of 13.8 versus 14.8 months for GC and MVAC regimens respectively; median progression-free survival was 7.4 months for both groups, and response rates around 47% for both regimens. However, the toxicity profile of GC was favourable compared to MVAC. Comparing MVAC to GC, neutropenic sepsis (12% versus 1%), grade 3/4 mucositis (22% versus 1%) and drug-related death (3% versus 1%) were all more common in the MVAC-treated group. While GC is a less toxic regimen, most guidelines support the use of either as first-line therapy in the setting of inoperable locally advanced bladder cancer or metastatic disease.

Given that the mean age at diagnosis of bladder cancer is 73, and smoking is one of the prominent risk factors, a significant proportion of patients have comorbidities, such as chronic obstructive airways disease, coronary heart disease and chronic kidney disease, which can impact on their medical fitness to receive cisplatin-based chemotherapy (most guidelines use a cut-off estimated glomerular filtration rate of >60).

For those patients not fit enough to tolerate cisplatin-based chemotherapy (Box 1), a common alternative is the combination of gemcitabine and carboplatin, which in the EORTC 30986 study was shown to give a 41% overall response rate, median overall survival of nine months, and six months progression-free survival. Other non-platinum-based regimens, such as gemcitabine in combination with a taxane, have been evaluated in phase 2 studies in this setting and shown to have efficacy, although response rates and overall survival are lower than in those receiving platinum-based chemotherapy.

As well as those not fit enough for a platinum-based regimen, some patients may have significant comorbidities or poor performance status (3 or 4), in which case best supportive care rather than active systemic therapy is recommended. Early palliative care input is crucial. Management for these patients is symptom-driven and could include radiotherapy for pain and urological intervention for obstructive symptoms. The multidisciplinary team and, most importantly, the clinical nurse specialist are key in directing the care of these patients.

Although the figures given above represent typical response rates and survival with chemotherapy, there is a degree of heterogeneity in these responses. Some patients seem to have tumours that are very sensitive to chemotherapy; others have disease that seems not to respond at all. Interestingly, it has been proposed that there are a variety of molecular subtypes of bladder cancer, which may help to explain the differing levels of chemotherapy sensitivity. Much like in breast cancer, distinct basal and luminal subtypes of bladder cancer have been identified. Basal type cancers appear, on the whole, to be more aggressive but more likely to respond to chemotherapy versus luminal tumours.

Therefore, for those patients not fit enough for chemotherapy, and those who may have a molecular type of bladder cancer not likely to be sensitive to chemotherapy, there remain no first-line treatment options beyond symptom control and best supportive care. It may be that immunotherapy can provide an alternative treatment for some of these patients.

SECOND-LINE CHEMOTHERAPY

There are very few complete and sustained responses to first-line chemotherapy, with most patients progressing after around eight months. Various chemotherapy agents and combinations have been used post platinum failure, although all with only modest benefits. Studies of single-agent treatment show a response rate of 6–29%, with a mean survival of 5–13 months. Combination chemotherapy generally improves response rates (0–61%) without improving overall survival (4–14 months). Current UK guidelines support the off-licence use of gemcitabine in combination with either paclitaxel or carboplatin. These data underline the urgent need for effective new treatments, and there is growing evidence that immunotherapy agents are active in this setting.

Box 1. Defining medically frail patients unfit for cisplatin-based chemotherapy

At least one of the following criteria must be present:
- Performance status >1
- GFR <60ml/min
- Grade 2 audiometric loss
- Peripheral neuropathy
- NYHA class III heart failure
PD-1/PD-L1 inhibitor  | Response rate | Trial phase |
---------------------|--------------|------------|
Atezolizumab        | 15%          | 2          |
Avelumab            | 18%          | 1b         |
Durvalumab          | 17%          | 1/2        |
Nivolumab           | 20%          | 2          |
Pembrolizumab       | 21%          | 3          |

Table 1. Response rates for checkpoint inhibitors in second-line therapy for bladder cancer

IMMUNOTHERAPY

Immune checkpoint inhibitors have revolutionised outcomes for various cancers since their introduction over the past decade, including some durable responses and even cures for some patients. These monoclonal antibodies target inhibitory pathways, often upregulated in malignancies, which prevent immune cells from eradicating tumour cells. These immunotherapy treatments have demonstrated impressive results in melanoma, renal cell, lung, and head and neck cancer, as well as Hodgkin lymphoma. The immunogenicity of bladder cancer was shown 40 years ago when the use of Bacillus Calmette-Guerin (BCG) was shown to prevent recurrence in localised non-muscle-invasive bladder cancers.

Recent advances also indicate a potential susceptibility of bladder cancer to immune checkpoint inhibitors, with studies showing urothelial bladder cancer demonstrating high expression of immune checkpoint molecules such as programmed cell death-1 ligand (PD-L1). Consequently, there has been increasing interest in assessing the efficacy of treatments targeting the programme cell death-1 pathway in bladder cancer with monoclonal antibodies against the PD-1 receptor and its ligand PD-L1. Moreover, alternative immune checkpoint molecules such as cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) are targeted with monoclonal antibodies such as ipilimumab, currently licensed for treatment of advanced melanoma. Studies investigating the role of CTLA-4 inhibitors in the context of bladder cancer are also underway, as well as the use of combined anti-CTLA-4 and anti-PD-1 immunotherapy.

Second-line treatment

Over the past 18 months, five antibodies targeting the PD-1/PD-L1 axis (atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab) have gained FDA approval for the treatment of patients with advanced bladder cancer who have progressed on or after platinum-based chemotherapy. Only pembrolizumab has been shown to improve overall survival in a randomised trial so far, while the other agents were given accelerated approval based on impressive response and survival outcomes in phase 1/2 clinical trials. Although no direct comparison between the various immune checkpoint inhibitors exist, response rates for these agents vary between 15% and 25% (Table 1).

Focusing on the only randomised phase 3 trial published so far, results from the Keynote-045 study, which compared pembrolizumab to second-line chemotherapy (physician choice) in patients after platinum-based chemotherapy, showed a significant overall survival benefit for pembrolizumab of 10.3 versus 7.4 months. Pembrolizumab also demonstrated higher response rates to treatment (21.1% versus 11.0%) and significantly fewer serious adverse events (15% versus 49.4%). Although the overall response rate of 21% appears modest, it is clear that patients with an objective response often have durable clinical benefit from these drugs, with 72% of patients showing an ongoing response at the time of data cut-off (compared to 35% for the chemotherapy cohort).

Predicting response

A remaining issue is that we are currently unable to predict which patient will respond and benefit from immunotherapy. PD-L1 expression has been investigated as a potential predictive biomarker in the trials referred to, but so far this has not resulted in practice-changing selection markers on which we can base treatment decisions. Although bladder tumours with high expression of PD-L1 are more likely to respond to immunotherapy agents compared to tumours with low or no PD-L1 expression, it is by no means a binary distribution, and multiple reports of patients with PD-L1 negative tumours who subsequently benefit from PD-1/PD-L1 directed therapy exist. As a result, the approval of these agents is not dependent on tumour biomarker expression and research into this field is ongoing.

First-line treatment

The role of immune checkpoint inhibitors as a first-line treatment option for advanced bladder cancer remains subject to ongoing trials. As shown, responses to first-line platinum-based chemotherapy are short lived and therefore improved treatment options are needed urgently. A number of large randomised phase 3 trials comparing chemotherapy with immunotherapy, including combination therapies, in the first-line setting are ongoing, with results expected in the next 18 months. Initial results from the Keynote-052 trial (pembrolizumab in those ineligible for platinum-based chemotherapy) demonstrate a response rate of 29%. Of note, this cohort included nearly 30% of patients over the age of 80 years and 21% had liver metastases. At present, the role of immunotherapy in the first-line setting is not yet fully established, and wherever possible patients should be enrolled into clinical trials.

Side-effects

While single-agent checkpoint inhibitors are relatively well tolerated, immune-mediated side-effects are common. Side-effects can occur in any organ that contains immune cells and most commonly include fatigue, nausea and rash. More severe side-effects include pneumonitis,
hepatisis, colitis and endocrinopathies. If severe, these may require temporary cessation of the agent, corticosteroid treatment and hospitalisation. However, overall severe treatment-related side-effects are less common with checkpoint inhibitors compared to chemotherapy (15% versus 50% of patients), as is treatment-related discontinuation of therapy (5.6% versus 11%). In contrast to cytotoxic chemotherapy, myelosuppression and neutropenic sepsis are not a concern following immunotherapy. The use of immune checkpoint inhibitors, as either single agent or combined anti-CTLA-4 and anti-PD-1/PD-L1 therapy, has rapidly expanded over the past five years. As a result, oncologists and nurse specialists have had to rapidly increase their knowledge on the safe management of these patients. It is crucial, however, that all healthcare professionals who care for these patients receive appropriate training, since the management of immune-related side-effects starts with early recognition and treatment.

**TARGETED THERAPY**

Molecular analysis of bladder tumours has identified various genetic mutations and alterations, a number of which can be targeted, including PTEN deletions, TP53 and fibroblast growth factor receptor mutations. Drugs targeting these specific mutations are currently undergoing trial evaluation either as a single agent or in combination with checkpoint inhibitors. At present there is no established role for these targeted therapies in the management of bladder cancer, although promising results from single agents have been reported.

**CONCLUSION**

For many years, platinum-based chemotherapy has been the treatment of choice for inoperable and metastatic bladder cancer. While prognosis for patients with advanced disease remains poor, immunotherapy appears, at least for a subset of patients, to offer improved survival. Further research establishing biomarkers to tailor treatment choice according to each patient’s own tumour profile will likely enhance outcomes. Combination immunotherapy may deliver additional benefits, although potential severe side-effects will require careful consideration in an ageing, often medically frail patient cohort. The landscape of bladder cancer treatment is changing rapidly, and we hope to see this demonstrated by improved patient outcomes in the UK in the not too distant future.

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**REFERENCES**


