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VINFLUNINE IN METASTATIC BLADDER CANCER

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Abstract: *Vinflunine is the only drug tested in a phase III trial and, to date, approved in the second line chemotherapy for advanced or metastatic bladder cancer. We present a case report of a long-surviving man with metastatic bladder cancer treated with vinflunine and a review of literature in this setting.*

Keywords: *Metastatic bladder cancer, Chemotherapy, Vinflunine.*

INTRODUCTION

Bladder cancer is the ninth most common cancer worldwide and the most frequent of genitourinary tract[1]. The majority of bladder cancers are diagnosed at an early stage, i.e. confined to the urothelium and lamina propria. These patients are often managed successfully with local therapies[2,3]. Approximately one-third of patients present a tumour that invade the muscularis propria and/or beyond. Despite aggressive management of localized urothelial carcinoma, up to 50% of patients will develop metastatic disease, and another 20% will have metastatic disease at presentation. Cisplatin-based combination chemotherapy represents the standard of care for fit patients with adequate renal function[4-6]. Although RRs to this approach is 50%, these responses are rarely durable. In the second-line setting, there are no effective and well-tolerated treatment options. To date, the only drug tested in a phase III trial against best supportive care is the microtubule-targeted agent Vinflunine, which showed an overall RR (ORR) of 8.6%, PFS of 3.0 months, and OS of 6.9 months. Although it is approved in Europe, vinflunine has not been widely adopted due to significant toxicity, including neutropenia, fatigue, anemia, and constipation[7,8].

Case presentation

A 56-year-old man was referred to our institution in August 2009 for histologically confirmed urothelial bladder carcinoma with muscularis infiltration. The staging of the disease was negative for distant metastases and patient had undergone radical cystectomy with orthotopic neo-bladder. The histology exam was poorly differentiated carcinoma, infiltrating the bladder wall-thickness up to perivisceral fat, pT3b G3 pN0. The patient reported a medical history of hypertension and diabetes mellitus type II. In November 2009 he started adjuvant chemotherapy with gemcitabine (1250 mg/m^2 on days 1, 8) and cisplatin (70 mg/m^2 on day 1) intravenously every 21 days for

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four cycles. In September 2010, for the appearance of intense pelvis pain symptoms, patient performed a bone scan that showed a pathological hyper accumulation in left ischio-pubic branch, confirmed to the total body CT. The patient started palliative radiotherapy (RT) for a total of 30 Gy and subsequent first-line chemotherapy with gemcitabine (1250 mg/m^2 on days 1, 8), cisplatin (70 mg/m^2 on day 1) intravenously every 21 days for six cycles + Zoledronic acid (4 mg). A radiological stable disease, as best response, according to RECIST criteria, was obtained at the end of treatment with a good pain control. In August 2011, the PET-CT performed for restaging disease, showed the appearance of new bone lesions at ninth right rib and first lumbar vertebra (L1) with the progression of known lesion at the left ischiopubic branch (SUV 6.7). At that time, patient had an European Cooperative Oncology Group performance status (ECOG-PS) of 2 for tumour-related pain. In September 2011, patient started second-line chemotherapy with vinflunine intravenous 280 mg/m^{2}at the first cycle, increased to 320 mg/m^{2}at the second cycle, continuing zoledronic acid 4 mg IV every 21 days. A radiological partial response, defined as best response according to the RECIST criteria, was obtained, after 6 cycles of treatment. This clinical and radiological response was maintained in subsequent disease restaging performed every 3 months, with clinical improvement (ECOG-PS: 0), pain relief and absence of significant side effects. Treatment (320 mg/m^2) was continued until July 2012 (14 total cycles) without dose modifications, and thenvinflunine was interrupted because of disease progression and a decline of the patient's clinical condition. He died in October 2012, with a PFS of 10 months and OS, after the start of vinflunine, of 13 months.

Discussion

In the second-line setting, there are no effective and well-tolerated treatment options. To date, the only drug tested in a phase III trial against best supportive care is the microtubule-targeted agent Vinflunine. Bellmunt et al. compared vinflunine plus best supportive care to best supportive care alone in a randomized phase III trial for patients who had previously received a platinum containing regimen. The vinflunine arm had a significantly longer median overall survival of 6.9 months vs. 4.6 months for best supportive care alone, which reached statistical significance and an overall RR (ORR) of 8.6%. The study included quality of life measures, and the chemotherapy arm did not reduce quality of life in this palliative setting[6,7]. Although it is approved in Europe, vinflunine has not been widely adopted due to significant toxicity, including neutropenia, fatigue, anaemia, and constipation[6,7].Overall Survival after progression on first-line therapy with platinum is usually very short and accompanied by a rapid deterioration of the PS and the quality of life (QOL).Different chemotherapeutic agents were evaluated in this setting, such as nab-paclitaxel, pemetrexed, gemcitabine, pegylated liposomal doxorubicin, taxotere, etc, but no one to date has shown a significant increase in overall survival[9-18]. Also Targeted therapies have been investigated for use in patients with advanced or metastatic urothelial cancer after failure of prior platinum-containing chemotherapy regimen, alone or in combination with chemotherapy. The most active area under investigation is targeting the VEGF pathway, MTOR inhibition, EGFR blockade, FGFR inhibitor, inhibitor of the proteasome pathway, immune checkpoint inhibition[19-30]. At this time, despite promising preclinical activity, failed to show activity in a second-line trial in unselected patients, indicating the importance of patient selection in the development of these targeted therapies. New targets include CD105, polo-like kinase-1, phosphatidylinositide 3-kinases (PI3K), transforming growth factor β receptor/activin receptor-like kinase β, estrogen receptor, cell-cycle checkpoint pathways such as Chk1 and 2, the hepatocyte growth factor receptor (HGFR or MET), insulin-like growth factor 1R(IGF1R)[19] and immune checkpoint. At recent ASCO 2015 was presented the antitumor activity of pembrolizumab in patients with recurrent or metastatic urothelial cancer, assessed in a cohort of KEYNOTE-012 (Clinicaltrials.gov: NCT01848834), showed acceptable safety and tolerability and provides promising antitumor activity in patients with advanced urothelial cancer[31]. The preliminary results of the phase II Trial, evaluating efficacy of Temsirolimus (Torisel®) in second line therapy for patients with advanced bladder cancer, providing the first clinical evidence of a potential benefit of temsirolimus for the treatment of relapsed bladder cancers. Ancillary study is ongoing to investigate the mutational status of genes, which are involved in the PI3K/AKT/mTOR signalling pathway in order to identify a predictive signature of response to temsirolimus in bladder cancer[32].

However, there are no new drugs approved in this setting that improve significantly overall survival. The main problems that make difficult to find new effective therapies are the biasin the design of clinical trials, particularly in the patients' selection to be enrolled and in their stratification in different subgroups, and that the majority of these trials are small, single-arm, single-center, nonrandomized, phase 2 involving 1 to 3 study

sites. Previous therapy with cisplatin is another important issue to consider for survival in the second-line setting irrespective of the actual second-line therapy. The established prognostic factors for improved survival include good PS and absence of visceral metastases or anaemia[33]. Sonpavde G et al[34] observed that shorter time from prior cisplatin therapy to start of subsequent therapy also portended worse survival in the second-line setting. The reduction in the risk of death obtained with vinflunine was similar in the cisplatin and non-cisplatin arms. Previous cisplatin use correlates with improved survival; however, upon further multivariate analysis, this improvement may be best attributed to those patients having more favourable prognostic criteria such as better PS and absence of visceral metastasis or anaemia. Vinflunine remains the only agent to demonstrate an improvement in OS in the second-line treatment of bladder cancer and should be accepted as the standard of care with the recognition that the median 2-month survival benefit is modest, and the investigation of novel agents that target driver pathways is imperative[35].

Our case report demonstrates how vinflunine used in second line has been able to improve the quality of life of the patient and improve its survival.

CONCLUSIONS

In the second-line setting, there are no effective, well-tolerated treatment options. To date, the only drug tested in a phase III trial against best supportive care is the microtubule-targeted agent vinflunine. Molecularly targeted approaches and immunotherapy remain under active investigation but further work is needed before they may be routinely used against advanced bladder cancer. Hence the need to design clinical trials stratifying patients according to prognostic factors, chemotherapy-resistant disease progressing within 6 months of first-line therapy and chemotherapy-sensitive disease progressing more than 6 months after first-line therapy and in the case of targeted therapies, on the expression of the target under investigation to the tumour sample.

Conflict of Interests: The Authors declare that they have no conflict of interests.

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