Long-term response in advanced bladder cancer involving the use of temsirolimus and vinflunine after platin resistance

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Relapse after initial first-line chemotherapy shows a poor prognosis in metastatic urothelial cancer. Currently, several chemotherapeutic agents and targeted drugs are under evaluation for platin-resistant advanced urothelial carcinoma. Vinflunine has been approved for second-line treatment in this indication. We present a patient with initial T4 advanced and subsequently metastasized bladder cancer, who has shown prolonged survival of 44 months after radical cystectomy. During her clinical course, the patient received two different platinum-containing therapies, temsirolimus within a phase II protocol and subsequent vinflunine chemotherapy. Treatment duration was 15 weeks with temsirolimus and 9 weeks with vinflunine, respectively, with a stable disease period of 3.8 months under temsirolimus therapy. This case is an example of how patients can derive a survival benefit from adequate sequencing of surgery and medical treatment including the newest therapies, even in advanced disease.

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Introduction

Urothelial carcinoma of the bladder is the fourth most common cancer in men and the ninth most common in women [1]. Regional or distant metastases are found in approximately 15% of patients who initially present with bladder cancer, whereas infiltrating tumors will develop distant metastases in up to 30–40% of cases, despite standard surgical treatment with radical cystectomy.

The 5-year survival rates for patients with stage T2 and T3 disease are 73 and 40%, respectively. Bladder cancer leading to death is mainly related to distant metastatic spread. Today, the median overall survival (OS) is approximately 14 months for patients with metastatic bladder cancer when treated according to the current recommendations [2]. Prevention of metastatic disease by implementing neoadjuvant and/or adjuvant therapy approaches remains worthwhile. Most of the systemic therapies in urothelial cancers have revolved around the management of advanced/metastatic disease. Partial and/or complete responses have been reported for significant numbers of patients using single chemotherapeutic agents and combinations as first-line treatment approaches. The two first-line chemotherapy regimens for metastatic urothelial carcinoma that have been widely adopted consist of either cisplatin and gemcitabine, or the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) combination [3–5]. Sternberg *et al.* [6] could show an additional benefit in progression-free survival (PFS), complete response, and overall response for high-dose MVAC over conventional MVAC in a phase III trial, thus offering another front-line option for this indication.

With increasing use of neoadjuvant and adjuvant chemotherapy in localized urothelial carcinoma, the proportion of patients with metastatic cancer with cisplatin refractory disease is predicted to rise. Relapse after initial chemotherapy shows a poor prognosis. Effective second-line bladder cancer therapy has been an unmet medical need with nearly no data favoring monotherapy, polychemotherapy, or alternating therapy. However, several drugs have been tested or are currently under evaluation for platin-resistant advanced urothelial carcinoma. Several of these compounds showed response rates between 10 and 20% in single-agent phase II clinical trials.

The microtubule inhibitor vinflunine has shown survival benefit in a multivariate analysis of a phase III clinical trial in platinum-pretreated progressive metastatic urothelial cancer comparing the compound as a single agent with best supportive care and is therefore a reasonable treatment option in the second-line setting [7–9].

We present the case of a patient with platin refractory metastatic urothelial cancer who showed prolonged OS along his clinical course. The patient received temsirolimus after platin failure within a phase II clinical trial, followed by vinflunine after the drug's approval.

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Case presentation

A 58-year-old female Caucasian patient (Eastern Cooperative Oncology Group performance score 1) nonsmoker without professional predisposition was primarily diagnosed with bladder cancer in October 2006. After one session of transurethral resection-B revealing a pT2G3 urothelial carcinoma of the urinary bladder, the patient underwent radical cystectomy with creation of an ileal neobladder. Definitive histological evaluation revealed a pT4a pN0 (0/12) cM0 pL1 pV1 R1 G3 tumor. As a result of this unfavorable surgical outcome with an R1 resection and relevant microvascular invasion (pL1, pV1), this tumor was predicted to have a high risk of recurrence and/or dissemination. Only 3 months after radical surgery, a vaginal recurrence was diagnosed and again local resection was performed requiring postponement of the initially planned adjuvant chemotherapy with gemcitabine/cisplatin.

In August 2007, an undiversion from neobladder into the pouch had to be performed after the resection of recurrent abdominal tumor masses. Directly after this surgical treatment, chemotherapy with gemcitabine and cisplatin was started. The patient received intravenous gemcitabine at a dose of 1250 mg/m^2 on days 1 and 8, and intravenous cisplatin at a dose of 70 mg/m^2 on day 2. Treatment courses were repeated every 21 days. Cisplatin-based therapy had to be stopped after two cycles due to severe side effects. Therapy was continued using gemcitabine mono after the following regimen: intravenous gemcitabine at a dose of 1250 mg/m^2 on days 1 and 8. Treatment courses were repeated every 21 days.

During this therapy cycle, a subcutaneous metastasis on the mons pubis was excised in toto (R0) in February 2008. A second-line chemotherapeutic approach was performed with six cycles of carboplatin and gemcitabine polychemotherapy between April and December 2008. The patient received chemotherapy with intravenous gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8, and intravenous carboplatin at a dose calculated after the actual area under the curve 5 on day 2. Treatment courses were repeated every 21 days. The result of restaging was partial response. Nevertheless, progression was detected in abdominal lymph nodes. The patient received palliative radiation until March 2009. After this treatment, the staging showed again partial response. In June 2009, new metastatic spread to the iliacal lymph nodes and liver was visible on a staging CT scan. The patient was therefore enrolled in a phase II study with temsirolimus after platinum-containing treatment failure. The patient received 15 cycles of weekly intravenous temsirolimus (25 mg per cycle) between September 2009 and January 2010 with only minimal progress being visible. The treatment had to be stopped due to severe side effects, such as grade III mucositis and massive reduction of performance status and quality of life. However, at the point of temsirolimus interruption the patient was deemed to have stable disease. The patient then started treatment with the recently approved microtubule inhibitor vinflunine (320 mg/m^2 every 3 weeks). Between February and March 2010, she received three cycles of treatment, after which a staging computed tomographic scan showed progression of disease with new metastasis to the liver, bones, and mediastinal lymph nodes. As the last therapy, the patient received best supportive care in April 2010. Further problems and complications of the fast progressive disease were liver pain due to metastasis, lymph edema, and progressive renal insufficiency with intermittent dialysis. The patient died in June 2010, 44 months after the initial diagnosis of locally advanced bladder cancer.

Discussion

Median survival in a patient with metastatic urothelial carcinoma is 12–14 months. Interestingly, the patient presented here survived 44 months after initial diagnosis of locally advanced bladder cancer, which throughout the clinical course developed metastatic spread. Thus, the patient could survive her expected stage-adapted survival rate for more than 2 years. The case remains exceptional, as survival could be prolonged using different means of therapy: three surgeries in terms of metastasis resection in addition to the initial radical cystectomy, a radiation therapy approach, and four lines of chemotherapy (Table 1).

In the last few years, new biologic agents have raised the expectations in the second-line treatment of relapsed metastatic transitional cell carcinoma of the urothelium (TCCU) after platin-containing first-line therapy. Patients should be enrolled in well-designed studies to define the role of these targeted therapies, to improve clinical outcome, and to individualize treatment. However, as eligibility criteria for reported phase II trials have varied considerably and heterogeneous populations have been enrolled, comparison of outcomes across trials remains difficult. To date, in the second-line setting, vinflunine is a reasonable, and in Europe, recently approved option [7].

Targeted agents have been proven to be beneficial in several neoplasms. However, in advanced bladder cancer, there is still little information about their oncologic activity.

Epidermal growth factor receptor and HER-1/2 are potential targets that are known to be overexpressed in TCCU. New agents such as lapatinib and trastuzumab have been investigated in phase II clinical trials in the second-line setting [10,11]. Sorafenib and sunitinib have been tested in the setting of advanced TCCU with limited benefit for the patients [12,13].

Despite less prominent in-vitro data in TCCU, it is well established that phosphatase and tensin homolog mutations are present in approximately 30% of patients with

Table 1 Summary of the clinical course over 44 months from initial diagnosis

Treatment modalities	Specific treatment	Time span	Effectiveness
Surgery	Radical cystectomy with ileal neobladder pT4a pN0 (0/12) cM0 pL1 pV1 Rx G3	October 2006	CR
Surgery	Undiversion to pouch resection of recurrence tumor mass in abdomen	July 2007	PR
First-line chemotherapy	Gemcar/cisplatin Gemcitabine mono	August 2007–October 2007 October 2007–February 2008	Stop after 2 months (two cycles)
Surgery	Excision of a subcutaneous metastasis on mons pubis	February 2008	CR
Second-line chemotherapy	Carboplatin and gemcitabine	April until December 2008	Six cycles, PR
Radiation	Palliative radiation	Until March 2009	Progress in June 2009
Third-line chemotherapy	Temsirolimus	September 2009 until January 2010 (15 infusions over 15 weeks)	15 cycles, PR stop due to severe side effects
Fourth-line chemotherapy	Vinflunine	February until March 2010 (three infusions over 9 weeks)	Three cycles, staging after 9 weeks: massive progress
Best supportive care	Best supportive care	March until June 2010	Deceased June 2010

Chemotherapeutic/medical treatment approaches are marked in bold.
CR, complete response; PR, partial response.

TCCU and that the phosphatidylinositol 3-kinase pathway regulates TCC cell invasion [14]. Animal studies suggest remarkable antitumor activity in TCCU both *in vitro* and *in vivo* for everolimus [15]. Thus, mamalian target of rapamycin (mTOR) inhibition may be an attractive therapeutic strategy for this disease. However, the development of clinical trials with mTOR-inhibitors in this setting has been quite slow. Currently, there are few ongoing clinical trials evaluating mTOR-inhibitors in metastatic TCCU. A current phase II trial aims to determine the response rate of everolimus as second-line treatment in patients with progressive urothelial cancer who have received previous cytotoxic chemotherapy (*http://clinicaltrials.gov/ct2/show/NCT00805129*). The trial was presented at this year's American Society of Clinical Oncology-Genitourinary meeting; a 2-month PFS rate of 50% will be considered not promising, whereas a 70% 2-month PFS will be rated promising. At our institution, temsirolimus is currently under evaluation in a phase II trial in patients with metastasized TCCU after platin-containing therapy. Primary endpoints are OS and quality of life. The study has completed accrual and data are currently analyzed. In contrast to the current second-line studies, a phase I/II single-arm trial to evaluate the combination of cisplatin and gemcitabine with temsirolimus for patients with advanced TCCU (TOTEM) focuses on mTOR-inhibition in the first-line setting (*http://www.controlled-trials.com/ISRCTN31546330*).

Without any doubt, describing single patients from ongoing studies remains critical. However, in particular cases they are worth reporting. Under temsirolimus therapy, the patient initially suffered comparable adverse events as reported from patients with metastatic renal cell carcinoma, such as mucositis, fatigue, and anemia, which were all grade I/II in nature and medically manageable. Oncologic activity could be attributed to temsirolimus as the patient had a partial response over 15 weeks, but unfortunately therapy was interrupted due to increasing severe side effects, such as grade III mucositis and massive reduction of performance score and quality of life.

During the time of temsirolimus treatment, vinflunine received official approval, thus giving us the opportunity to offer this patient another line of therapy. The sequence temsirolimus–vinflunine is not likely to reoccur in the near future; thus, we consider it worth mentioning in particular with regard to the feasibility of this sequence. In addition to the known adverse event profiles of temsirolimus and vinflunine, the sequenced therapy of both drugs was moderately tolerated. In conclusion, the patient received 15 weeks of temsirolimus treatment and, subsequently 9 weeks of vinflunine, a total of 24 weeks of therapy with targeted agents. With regard to the oncologic outcome, this suggests that temsirolimus seemed to have antitumor activity resulting in stable disease over 15 weeks. Official approval of vinflunine in the setting of metastasized urothelial carcinoma after failure of platinum-containing therapy dates back a few months only. Therefore, clinical experiences from daily oncological practice are limited and can be of value for physicians treating patients in comparable clinical settings. Second-line clinical trials are likely to play a role in the future for patients with advanced TCCU. Thus, it seems worthwhile to report cases of patients who receive the officially approved drug vinflunine following whatever previous study medication/combination. Therefore, these possible sequences should be reported to hold all possible therapeutic approaches for the patients. This report could encourage other researchers to describe comparable sequencing approaches. In this particular patient, vinflunine was given as fourth-line treatment at a reduced Performance Score and at highly progressive disease. Compared with the phase III trial reported by Bellmunt *et al.* [7] with a median PFS of 3 months or three treatment cycles respectively, the patient reported here almost reached the same treatment duration and the predicted oncologic benefit of 2.4 months of OS.

Regardless, the patient received the three cycles over 9 weeks at a moderate adverse event profile. Treatment had to be discontinued due to massive progress; thus, the application of the drug was not justified any longer. However, compared with the VFL 302 clinical trial the patient seems to reach comparable oncologic and functional results, even after three lines of chemotherapy extending her OS to 44 months since initial diagnosis.

Conclusion

Therapeutic options for patients with relapsed advanced urothelial carcinoma after platinum therapy are limited. Currently, ongoing clinical trials for this indication are mostly phase II in nature. Vinflunine seems to be an option for this indication and is officially approved. Sequenced treatment with vinflunine after temsirolimus seems feasible. Investigation of feasibility of other sequencing approaches including vinflunine seems worthwhile in particular for patients who initially had been included in second-line clinical trials to not deprive them of this therapeutic option.

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Conflicts of interest

There are no conflicts of interest.

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