

Combining Paclitaxel and Lapatinib as Second-line Treatment for Patients with Metastatic Transitional Cell Carcinoma: A Case Series

STÉPHANE CULINE, ZINEB SELLAM, LINDA BOUAITA, ELIAS ASSAF,
CATHERINE DELBALDO, MURIEL VERLINDE-CARVALHO and DAMIEN POUESSEL

Department of Medical Oncology, Henri Mondor Hospital, Créteil, France

Abstract. *Background:* Current first-line cisplatin-based combination chemotherapy regimens provide interesting response rates but limited impact on survival for patients with metastatic transitional cell carcinoma of the urothelium. Such results leave a significant patient population in need of salvage therapy. *Patients and Methods:* As the epidermal growth factor receptors 1 and 2 (EGFR and HER2) are frequently overexpressed in urothelial carcinoma, we explored the feasibility of a combination of paclitaxel (80 mg/m²/week) and lapatinib (1,500 mg orally daily) for six patients who were treated after failure of first-line platinum-based chemotherapy. *Results:* Only one out of six patients was able to receive the full doses during the first six weeks of treatment, while grade 2 or 3 diarrhea events required lapatinib dose reduction (one patient) or discontinuation (five patients), despite loperamide support. *Conclusion:* This combination is not recommended for this population of patients.

Metastatic transitional cell carcinoma of the urothelium (MTCCU) is a chemosensitive disease. First-line cisplatin-based combination chemotherapy is associated with improved outcomes compared to single-agent or non-cisplatin regimens. Current standard combinations include cisplatin, methotrexate, vinblastine and doxorubicin (MVAC) or cisplatin plus gemcitabine (GC). Both regimens provide similar efficacy, *i.e.* interesting response rates (about 50%), but limited impact on overall survival (about 14 months) (1). Such results leave a significant patient population in need of salvage therapy. Vinflunine has been recently approved in the European Union as second-line chemotherapy. In a phase III

trial comparing vinflunine with best supportive care (BSC) to BSC alone, an estimated difference in overall survival (OS) of 2 months was reached in the intent-to-treat population. However, a significant difference in OS was only seen after removing patients who had major protocol violations (2). Therefore therapy for patients who fail first-line cisplatin-based chemotherapy remains a highly unmet medical need.

In a phase II study led by the French Genito-Urinary Tumor group (GETUG), the activity of weekly paclitaxel as second-line chemotherapy was assessed in 45 patients with MTCCU. A low objective response rate (9%) along with a high rate of stabilization (38%) suggested limited impact as a single agent (3). As the epidermal growth factor receptors 1 and 2 (EGFR and HER2) are frequently overexpressed in urothelial carcinoma, the activity of lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER2, was studied as second-line therapy in 59 MTCCU patients. Among 34 assessable patients, the response rate was 1.7% and 18 (31%) patients achieved stable disease (4). Once again, these results suggested limited impact of lapatinib as a single agent.

In order to improve the efficacy of second-line treatments, enhancing the activity of cytotoxic agents by targeted therapies could be an interesting approach (5). However the toxicity profile should remain acceptable. We report here the feasibility of the combination of paclitaxel and lapatinib in six patients with MTCCU who were treated after failure of first-line platinum-based chemotherapy.

Case Series

Patients' characteristics are summarized in Table I.

Patient no. 1. In August 2007, a 51-year-old patient underwent a right radical nephroureterectomy for a pT4pN0, grade 3 upper-tract urothelial carcinoma. Six cycles of adjuvant chemotherapy (GC regimen) were given until February 2008. The patient developed liver metastases six months later. A partial response occurred after the delivery of five cycles of

Correspondence to: Stéphane Culine, Department of Medical Oncology, Hôpital Saint-Louis, Paris 7 University, 1, Avenue Claude Vellefaux, 75010, Paris, France. Tel: + 33 142494247, Fax: +33 142499895, e-mail: stephane.culine@sls.aphp.fr

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Table I. *Patients' characteristics.*

Patient	Primary tumor	First-line chemotherapy/ Response	Second-line chemotherapy					
			Metastatic sites of weekly infusions)	Paclitaxel (number of weeks)	Lapatinib (number	Reason for discontinuation	Tumor assessment	Survival (months)*
1	Upper tract	MVAC/PR	Liver	9	5	Grade 3 diarrhea	PD	7
2	Bladder	GCa/SD	Lung	6	4	Grade 3 diarrhea	PD	8
3	Bladder	GC/PR	RLN	6	6	Progressive disease	PD	8
4	Upper tract	GCa/SD	Pelvis	5	4	Grade 2 diarrhea	PD	4
5	Bladder	GCa/PD	Bone	10	6	Grade 2 asthenia	PD	5
6	Bladder	GCa / PR	RLN	7	3	Grade 2 diarrhea	PD	3
			MLN					
			Lung					
			Bone					

MVAC: Methotrexate, vinblastine, doxorubicine, cisplatin; GCa: gemcitabine, carboplatin; GC: gemcitabine, cisplatin; PR: partial response; SD: stable disease; PD: progressive disease; RLN: retroperitoneal lymph nodes; MLN: mediastinal lymph nodes. *As measured from day 1 of paclitaxel and lapatinib.

dose-dense MVAC. In June 2009, however, the patient experienced relapse, with increasing liver metastases along with lung metastases. He started second-line chemotherapy combining *i.v.* paclitaxel at 80 mg/m²/week and lapatinib at 1,500 mg orally daily. Treatment had to be stopped at day 18 because of grade 3 diarrhea despite loperamide support. Reduced doses of paclitaxel (60 mg/m²/week) and lapatinib (1,000 mg daily) were reintroduced on day 28. Lapatinib was stopped on day 38 because of unacceptable grade 2 diarrhea. The patient received three additional weekly administrations of paclitaxel. The radiological tumor assessment showed an increased number of metastases in the liver. The patient died of his disease in December 2009.

Patient no. 2. A radical cystectomy was performed in October 2004 for a 57-year-old patient for a pT2pN0, grade 3 urothelial carcinoma of the bladder. Lung metastases occurred in June 2008 and required six cycles of gemcitabine and carboplatin (GCa). Pulmonary lesions were considered as stable at the end of chemotherapy. Disease in retroperitoneal lymph nodes progressed in July 2009. Second-line chemotherapy combining *i.v.* paclitaxel at 80 mg/m²/week and lapatinib at 1,500 mg orally, daily was started. Treatment had to be stopped on day 17 because of grade 3 diarrhea despite loperamide support. Reduced doses of paclitaxel (60 mg/m²/week) and lapatinib (1,000 mg) were reintroduced on day 28 but lapatinib had to be stopped definitively on day 35 because of recurrent grade 3 diarrhea. Third-line treatment with vinflunine did not alter the course of disease and the patient died in February 2010.

Patient no. 3. In October 2004, a 58-year-old patient underwent a radical cystectomy for a pT2pN0, grade 3 urothelial carcinoma of the bladder. A pelvic recurrence occurred in July 2008. Seven cycles of GC provided a partial response. In August 2009, bone metastases required second-line chemotherapy. The patient was treated with *i.v.* paclitaxel at 80 mg/m²/week and lapatinib at 1,500 mg orally daily with loperamide support. Lapatinib doses were reduced to 1,000 mg daily from day 28 because of grade 1 diarrhea. Tumor assessment after two months of treatment (six cycles of weekly paclitaxel) showed progressive bone metastases. The patient died of progressive disease in April 2010.

Patient no. 4. A T3N3, grade 3 upper-tract urothelial carcinoma was diagnosed in December 2008 in a 72 year-old patient. First-line chemotherapy consisted of six cycles of GCa but no response was observed. Second-line chemotherapy with *i.v.* paclitaxel at 80 mg/m²/week and lapatinib at 1,000 mg orally, daily was started in September 2009. Despite loperamide support, lapatinib had to be stopped from day 25 because of unacceptable grade 2 diarrhea and grade 2 asthenia. After five weekly infusions of paclitaxel, liver metastases developed. The patient died of progressive disease in January 2010.

Patient no. 5. A T2N0 grade 3 urothelial carcinoma of the bladder was treated in August 2008, using a bladder-sparing approach with chemoradiotherapy in a 74-year-old patient. Metastatic disease developed in August 2009, with deposits in retroperitoneal and mediastinal lymph nodes, as well as

the lung. The disease progressed after three cycles of GCa. The patient started second-line chemotherapy with *i.v.* paclitaxel at 80 mg/m²/week and lapatinib at 1,000 mg orally daily in October 2009 with loperamide support. Grade 3 diarrhea occurred on day 13 and lapatinib had to be stopped. Lapatinib doses were reintroduced at 750 mg daily from day 28, but definitively stopped on day 45 because of recurrent grade 2 diarrhea. After 10 weekly administrations of paclitaxel, tumor assessment showed progressive disease. The patient died of progressive disease in February 2010.

Patient no. 6. A T2N2 grade 3 urothelial carcinoma of the bladder with retroperitoneal lymph node metastases was diagnosed in November 2008 in a 78-year-old patient. He achieved a partial response after first-line chemotherapy (six cycles of GCa), but bone metastases occurred four months later. Second-line chemotherapy with *i.v.* paclitaxel at 80 mg/m²/week and lapatinib at 1,000 mg orally daily was started in November 2009. Lapatinib had to be stopped from day 22 because of grade 3 diarrhea despite loperamide support. After seven weekly infusions of paclitaxel, disease progressed and the patient died in January 2010.

Discussion

It can be concluded from this case series that the combination of lapatinib (1,500 mg daily) and weekly paclitaxel (80 mg/m²) cannot be safely administered as second-line chemotherapy for patients with MTCCU. Indeed only one out of six patients was able to receive the full doses during the first six weeks of treatment, while grade 2 or 3 diarrhea events demanded lapatinib dose reduction (one patient) or discontinuation (five patients), despite loperamide support.

Lapatinib has been approved for the treatment of metastatic breast cancer in combination with capecitabine. Diarrhea is a well known side-effect of lapatinib and is recognized as the most frequently reported adverse event in patients with advanced solid tumors (6). A recent analysis has studied diarrhea events in patients who were treated in 11 trials with lapatinib as monotherapy, or its combination, with capecitabine or taxanes (7). At doses ranging from 1,000 to 1,500 mg/day when used as a single agent, 51% of 926 patients experienced diarrhea but only 6% reported grade 3 events and <1% grade 4 events. When lapatinib was combined with capecitabine or taxanes (paclitaxel or docetaxel), the proportion of diarrhea events was 65% and 48%, respectively. Grade 3 and 4 events occurred in 14% and <10% of patients, respectively. Overall, approximately 40% of patients treated with lapatinib monotherapy or combination therapy experienced a first diarrhea event within six days of treatment initiation, with a median duration of seven to nine days. Severe events were observed in a minority of patients, provided proactive monitoring and intervention were

introduced. When focusing on the combination of lapatinib with paclitaxel, it was shown that the frequency of diarrhea was related to the dose but not the serum concentration of lapatinib, suggesting that lapatinib toxicity evolves from a local effect on the gut epithelium. Pharmacokinetic interactions were reported when lapatinib was combined with paclitaxel. Co-administration of lapatinib and paclitaxel resulted in an approximately 20% increase in systemic exposure (area under the concentration-time curve) to both drugs. In contrast, lapatinib combined with either capecitabine or docetaxel did not result in detectable pharmacokinetic interactions (7). In a pilot study of adjuvant chemotherapy for breast cancer, the combination of paclitaxel (80 mg/m²) weekly with trastuzumab and lapatinib (1,000 mg daily) was also reported as not being feasible because of excessive diarrhea (8). Therefore, reducing the daily dose of lapatinib to 750 mg would be an option but the preservation of its efficacy is then questionable.

There is a clear rationale for targeting EGFR and HER2 in patients with MTCCU; members of the epidermal growth factor receptor (ERBB) family are overexpressed in the majority of patients. Although the prognostic significance of ERBB expression remains controversial, the combination of an EGFR, HER2, ERBB3 and ERBB4 expression profile may be a better prognostic indicator than any single family member alone (9, 10). The antiproliferative effect on transitional carcinoma cells has been demonstrated *in vitro* and *in vivo* with ERBB inhibition strategies including tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib) (5, 11) and monoclonal antibodies (cetuximab) (12). However, the results of clinical trials in patients with MTCCU have been disappointing so far. The combination of gefitinib with GC in 54 chemotherapy-naïve patients achieved a response rate of 43% and a median survival of 15 months, data which were very similar to those obtained with GC alone, suggesting that gefitinib did not substantially add to the efficacy of GC (13). In the second-line setting, only one patient experienced a partial response among 31 patients. The median survival was three months (14). Similar negative results were reported with lapatinib (4). An explanation for these failures may be the lack of appropriate selection criteria, such as activating point-mutations in the EGFR catalytic domain, for patients with non-small cell lung cancer or *HER2* gene amplification in patients with breast cancer. However EGFR mutations as well as *HER2* gene amplification are rare events in transitional carcinomas (15, 16).

To further proceed with therapies targeting the ERBB family in MTCCU, the French GETUG is conducting a randomized phase II study of MVAC with or without panitumumab, an EGFR monoclonal antibody, as frontline therapy in patients whose tumors have Kirsten rat sarcoma (*KRAS*) and Harvey rat sarcoma (*HRAS*) wild type genes.

Conflicts of Interest Statement

The Authors declare they have no conflicts of interest.

References

- 1 von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A and Arning M: Long-term survival results of a randomised trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 23: 4602-4608, 2005.
- 2 Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, Jagiello-Gruszfeld A, Karyakin O, Delgado FM, Hurlteloup P, Winquist E, Morsli N, Salhi Y, Culine S and von der Maase H: Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 27: 4454-4460, 2009.
- 3 Joly F, Houédé N, Noal S, Joly F, Houédé N, Noal S, Chevreau C, Priou F, Chinnet-Charrot P, Rolland F, Fléchon A, Henry-Amar M and Culine S: Do patients with advanced urothelial carcinoma benefit from weekly paclitaxel chemotherapy? A GETUG phase II study. *Clin Genitourin Cancer* 7: E28-E33, 2009.
- 4 Wülfing C, Machiels JP, Richel DJ, Grimm MO, Treiber U, De Groot MR, Beuzeboc P, Parikh R, Pétavy F and El-Hariry IA: A single-arm, multicenter, open-label phase 2 study of lapatinib as the second-line treatment of patients with locally advanced or metastatic transitional cell carcinoma. *Cancer* 115: 2881-2890, 2009.
- 5 McHugh LA, Sayan AE, Mejlvang J, Griffiths TR, Sun Y, Manson MM, Tulchinsky E, Mellon JK and Kriaevska M: Lapatinib, a dual inhibitor of ERBB-1/2 receptors, enhances effects of combination chemotherapy in bladder cancer cells. *Int J Oncol* 34: 1155-1163, 2009.
- 6 Burris HA III, Hurwitz HI, Dees EC, Burris HA 3rd, Hurwitz HI, Dees EC, Dowlati A, Blackwell KL, O'Neil B, Marcom PK, Ellis MJ, Overmoyer B, Jones SF, Harris JL, Smith DA, Koch KM, Stead A, Mangum S and Spector NL: Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 23: 5305-5313, 2005.
- 7 Crown JP, Burris HA 3rd, Boyle F, Jones S, Koehler M, Newstat BO, Parikh R, Oliva C, Preston A, Byrne J and Chan S: Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat* 112: 317-325, 2008.
- 8 Dang C, Lin N, Moy B, Come S, Sugarman S, Morris P, Abbruzzi A, Chen C, Steingart R, Patil S, Norton L, Winer E and Hudis C: Dose-dense doxorubicin and cyclophosphamide followed by weekly paclitaxel with trastuzumab and lapatinib in HER2/*neu*-overexpressed/amplified breast cancer is not feasible because of excessive diarrhea. *J Clin Oncol* 28: 2982-2988, 2010.
- 9 Chow NH, Chan SH, Tzai TS, Ho CL and Liu HS: Expression profiles of ERBB family receptors and prognosis in primary transitional cell carcinoma of the urinary bladder. *Clin Cancer Res* 7: 1957-1962, 2001.
- 10 Kassouf W, Black PC, Tuziak T, Bondaruk J, Lee S, Brown GA, Adam L, Wei C, Baggerly K, Bar-Eli M, McConkey D, Czerniak B and Dinney CP: Distinctive expression pattern of ERBB family receptors signifies an aggressive variant of bladder cancer. *J Urol* 179: 353-358, 2008.
- 11 Dominguez-Escrig JL, Kelly JD, Neal DE, King SM and Davies BR: Evaluation of the therapeutic potential of the epidermal growth factor tyrosine kinase inhibitor gefitinib in preclinical models of bladder Cancer. *Clin Cancer Res* 10: 4874-4884, 2004.
- 12 Perrotte P, Matsumoto T, Inoue K, Kuniyasu H, Eve BY, Hicklin DJ, Radinsky R and Dinney CP: Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. *Clin Cancer Res* 5: 257-265, 1999.
- 13 Philips GK, Halabi S, Sanford BL, Bajorin D and Small EJ: A phase II trial of cisplatin, gemcitabine and gefitinib for advanced urothelial tract carcinoma: Results of Cancer and Leukemia Group B (CALGB) 90102. *Ann Oncol* 20: 1074-1079, 2009.
- 14 Petrylak DP, Tangen CM, Van Veldhuizen PJ Jr., Goodwin JW, Twardowski PW, Atkins JN, Kakhil SR, Lange MK, Mansukhani M and Crawford ED: Results of the Southwest Oncology Group phase II evaluation (study S0031) of ZD1839 for advanced transitional cell carcinoma of the urothelium. *BJU Int* 105: 317-321, 2009.
- 15 Jacobs MA, Wotkowicz C, Baumgart ED, Neto BS, Rieger-Christ KM, Bernier T, Cohen MS, Libertino JA and Summerhayes IC: Epidermal growth factor receptor status and the response of bladder carcinoma cells to erlotinib. *J Urol* 178: 1510-1514, 2007.
- 16 Laé M, Couturier J, Oudard S, Radvanyi F, Beuzeboc P and Vieillefond A: Assessing HER2 gene amplification as a potential target for therapy in invasive urothelial bladder cancer with a standardized methodology: Results in 1005 patients. *Ann Oncol* 21: 815-819, 2010.

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