

Trastuzumab therapy in metastatic bladder carcinoma: The proof of concept

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Abstract

About 10% of metastatic urothelial carcinoma overexpress oncogenic HER2/neu receptor. Recent preliminary data suggest that patients with this particular molecular subset could benefit from trastuzumab therapy, which specifically targets the receptor and thus inhibits downstream activation pathway. Here we report a case illustrating this clinical benefit, with complete response reported as third line therapy in a heavily pretreated patient with diffuse metastatic urothelial carcinoma of the bladder. It also highlights the usefulness of 18-Fluorodeoxyglucose Positron Emission Tomography (18-FDG PET) as a biomarker for response to trastuzumab.

Keywords: trastuzumab; bladder cancer; HER-2/neu receptor; 18-FDG PET

Introduction

Metastatic bladder carcinoma is characterized by a particularly poor prognosis with existing therapeutic regimen. Best tumor responses have been reached with cisplatin-based combination chemotherapy as first line therapy. However, numerous patients are not eligible to cisplatin because of their age, poor general health status, congestive heart failure or renal dysfunction. Even in situations where condition for cisplatin is fulfilled, median survival hardly reaches 14 months [1]. In second line, there is no standard of care. Vinca alkaloid vinflunine demonstrated a survival benefit of 2 months compared to best supportive care, with overall response rate of only 8.6% with high-grade neutropenia reported in 50% of patients' [2]. In fact, the low responses and survival rates reported with conventional chemotherapy encouraged the development of molecular agents that would specifically target tumor cells. Most promising results were reported with pharmacological inhibitors against growth factor receptors. The HER2/neu receptor from the ErbB family is a tyrosine kinase receptor involved in cell growth and proliferation. It is overexpressed in numerous tumor models, resulting in constitutive activation of oncogenic pathway PI3kinase/Akt pathway. Humanized monoclonal antibody trastuzumab interferes with HER2/neu receptor and inhibits this downstream intracellular activation pathway. It has demonstrated significant benefits as

adjuvant therapy and in metastatic breast carcinoma overexpressing HER2/neu and more recently in metastatic gastric carcinoma [3]. The finding that HER2/neu is overexpressed in about 10 % of carcinoma of urothelial carcinoma suggests that it could be a valuable target in this setting [4, 5]. Here we report a case of an elderly patient receiving trastuzumab as third line therapy and experiencing complete metabolic response.

Case report

In February 2011, a 77 year-old male was addressed to our Institute for management of a metastatic urothelial carcinoma of the bladder. His main previous medical

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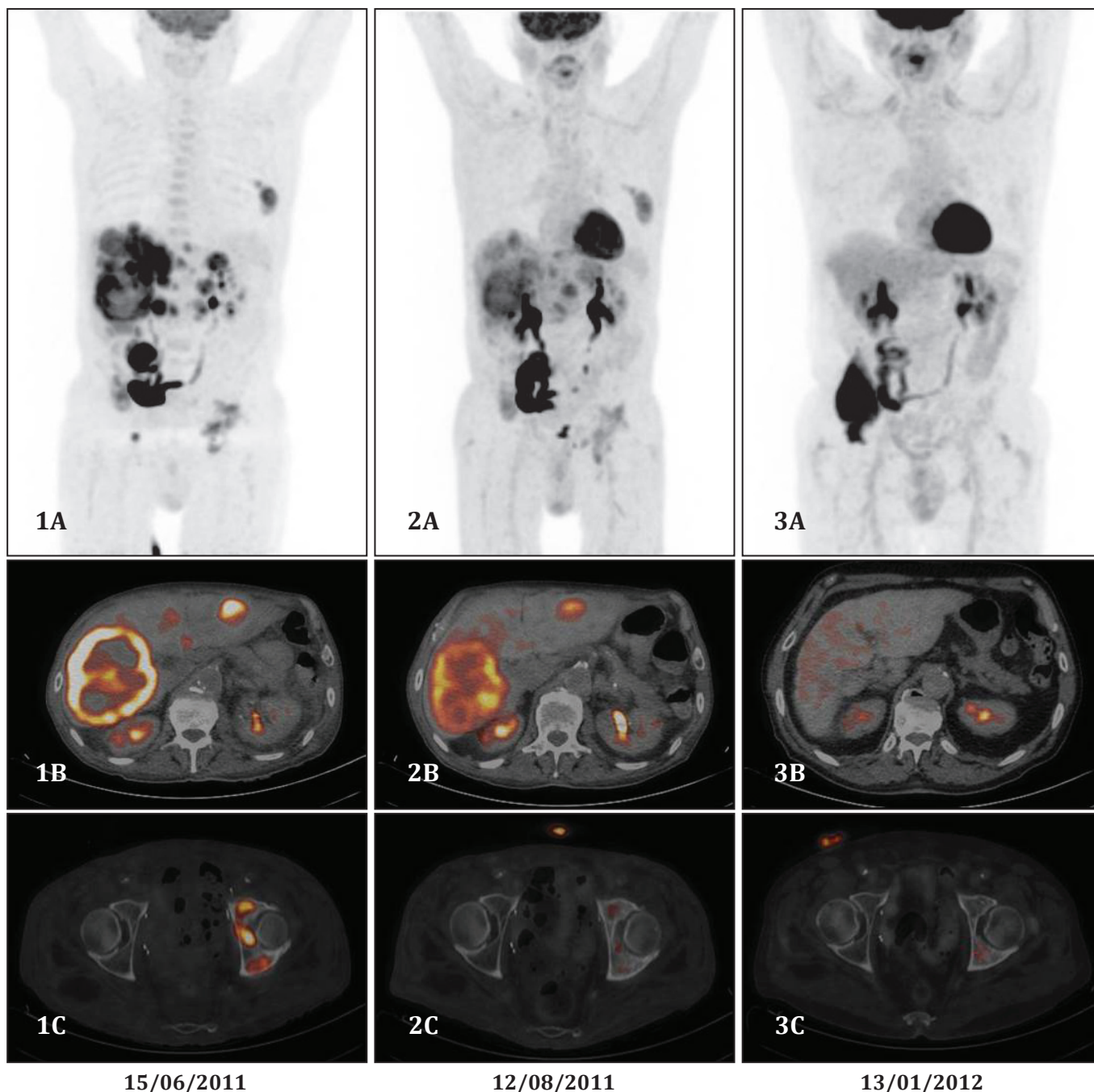
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history was grade II mitral insufficiency and tobacco consumer. He had received radical cystectomy and ureterocutaneostomy one year before for a bladder urothelial carcinoma, classified pT3aN0R0 and overexpressing HER2/neu, with an immunohistochemical staining scored as 3+. At time of metastatic relapse, 18-FDG PET showed multiple bone, hepatic, lymph node and pulmonary metastases. After four cycles GEMOX (gemcitabine, oxaliplatin) as first line chemotherapy, he experienced bone and hepatic progression, then was included in a clinical trial and received mTOR inhibitor. After one month, this treatment was disrupted because of decrease in general health status and tumor progression

(Figure 1). At this time and after multidisciplinary meeting, a third line therapy was decided with trastuzumab 2 mg/kg weekly after loading dose of 4 mg and paclitaxel 80 mg/m² weekly, from July 2011. After two cycles, there was an improvement in general health status and 18-FDG PET showed a 50 % decrease of FDG uptake for all metastases (Figure 2). The tumor response was confirmed after four cycles. After six cycles, there was disappearance of all hypermetabolic sites, suggestive of complete metabolic tumor response (Figure 3). The patient remains disease free after five months of trastuzumab as maintenance therapy. Echocardiography was performed every three months but no cardiac toxicity was reported.



Figures 1, 2, 3 Emission tomography (18-FDG PET) for assessing tumor response of trastuzumab: 18F-FDG-PET/CT studies presented with maximum intensity projection images (A) and axial PET/CT fusion images focused on hepatic (B), and left cotyloid bone target (C). Initial study (Figure 1) shows increased FDG uptake related to hepatic and bone metastases. Assessment after 2 cycles (Figure 2) shows a 50% decrease in SUV uptake. PET/CT after 6 cycles (Figure 3) shows a complete response of all metastases. Note that the patient has a ureterocutaneostomy.

Discussion

Currently available therapies for management of platinum-refractory metastatic bladder urothelial carcinoma are not satisfactory with response rate that do not exceed 10 % in second line with vinflunine and with no validated third line therapy. Jimenez et al. have investigated the prognostic significance of HER2/neu overexpression in muscle-invasive carcinoma of the bladder and reported no significant correlation between this event and survival. Of interest, they reported that overexpression in the primary tumor consistently predicted overexpression in a distant or regional metastasis [5]. Other authors have retrospectively found that HER2/neu overexpression was associated with higher tumor grade in patients undergoing cystectomy for locally advanced bladder carcinoma. They also found that disease-related survival was significantly worse in patients with HER2-overexpressing tumors compared to those without HER2/neu overexpression. This molecular subset was identified as an independent predictor for specific survival [6]. Actually, the true prognostic significance of HER2/neu overexpression remains debated and other authors reached opposite conclusions suggesting that overexpression in the context of paclitaxel-based chemotherapy could decrease the risk of death [7].

Preliminary data found that trastuzumab-based therapy could be safe and effective in metastatic urothelial carcinoma [8, 9]. Stronger clinical evidence came from a multicenter phase II trial published in 2007. In this study, 44 patients with HER2/neu positive urothelial carcinoma received trastuzumab combined with paclitaxel, carboplatin, and gemcitabine. Tumor responses were reported in 31 patients (70%) including five complete and 26 partial responses. Median time to progression and survival were 9.3 and 14.1 months, respectively [10]. More recently, a randomized phase II trial failed to show a significant benefit of adding trastuzumab to the combination of gemcitabine and platinum-based chemotherapy (cisplatin or carboplatin) in patients with stage IV urothelial cancer overexpressing HER2. Patients included in this study accounted for about 13 % of all patients tested on immunohistochemistry for the receptor. Of interest, survival was 33.1 months in patients receiving cisplatin + trastuzumab, versus 14.5 months in those receiving cisplatin without trastuzumab, suggesting that there is synergistic effect between both drugs and that baseline platinum treatment could have an impact on the benefit of combination [11].

One concern about trastuzumab was cardiac toxicity, which was reported in up to 22.7 % of patients [10]. In the randomized phase II trial described above, a decreased in left ventricular ejection was reported in 3.2 % of patients' [11]. Although our patient exhibited risk factors for cardiac toxicity, no decrease in cardiac contractile function was reported. Our observation illustrates that trastuzumab is particularly promising for metastatic bladder carcinoma,

with complete response reported as third line therapy in a heavily pretreated patient with diffuse metastatic disease.

This case also shows the utility of 18-Fluorodeoxyglucose Positron Emission Tomography (18-FDG PET) for assessing tumor response. There is growing evidence that 18-FDG PET/CT could be potentially useful in the management of bladder carcinoma. In a prospective study of PET/CT for bladder cancer in patients with negative conventional preoperative evaluations, sensitivity and specificity of 18-FDG PET/CT were 70 % and 94%, respectively. 18-FDG PET/CT detected occult metastases in 16 % of patients and PET finding were significantly correlated with survival [12]. To our knowledge, the place of 18-FDG PET/CT for early assessment of treatment response has not been addressed in the setting of bladder carcinoma. In the presented case, metabolic response after two cycles was predictive of a durable complete response lasting until last follow-up at five months, suggesting that metabolic imaging could be integrated as a biomarker for response to trastuzumab. This hypothesis warrants prospective confirmation.

Conclusion

There is not enough evidence level for incorporating trastuzumab in routine for treatment of bladder carcinoma. Further studies are needed to better determine its place in the management of bladder carcinoma, and more particularly after failure of platinum-based therapy. The integration of metabolic imaging as an early marker of treatment efficacy could help better determining which patients could most benefit from treatment.

Conflict of interest

The authors wish to express that they have no conflict of interest.

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