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Trastuzumab (Herceptin™) in Metastatic Transitional Cell Carcinoma of the Urinary Tract: Report on Six Patients

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Abstract

Objective: To report our preliminary experience with trastuzumab (Herceptin™) in the management of metastatic transitional cell carcinoma of the urinary tract.

Patients and methods: From november 2001 to august 2002, six patients received trastuzumab for metastatic transitional cell carcinoma of the bladder ($n = 5$) or renal pelvic cancer ($n = 1$). Trastuzumab was administered as a first-line therapy in 2 patients, a second-line therapy in 3, and a third-line therapy in 1. Each patient received a weekly intravenous administration of trastuzumab (initial dose of 4 mg/kg, followed by 2 mg/kg for other courses). A total of 6 courses was given. In 4 patients, trastuzumab was administered in association with paclitaxel (175 mg/m^2) and carboplatin (area under the curve of 6). One patient received the same combination of trastuzumab and paclitaxel, but without carboplatin. The remaining patient received only trastuzumab.

Results: The trastuzumab-based regimen achieved partial regression of metastases in all patients. Initial regression of metastases varied between 30% and 80%. The therapy was well tolerated. Treatment-related toxicity was moderate in all patients, except for one who experienced transient grade 4 neutropenia. Five patients died from cancer. The interval between trastuzumab initiation and patient death ranged from 8 to 22 months. The remaining patient was still alive 28 months after trastuzumab initiation.

Conclusions: Our preliminary data suggest that trastuzumab-based therapy may be safe and effective in metastatic transitional cell carcinoma of the urinary tract. Prospective trials are needed to further investigate this therapeutic option.

Keywords: Bladder cancer; Urothelial tumor; HER2; c-erbB-2; Therapeutic target

1. Introduction

The incidence of bladder cancer is increasing. Superficial bladder tumors are usually treated conservatively, while muscle-invasive tumors require cystectomy. Today, radical cystectomy for organ-confined cancer provides good oncological results, with a 10-year recurrence-free survival rate of approximatively 75% [1]. In opposite, bladder cancer with lymph nodes involvement and/or metastases is associated with an extremely poor prognosis. The 5-year survival rate of patients with nodal metastases is lower than 20% [2]. The development of new chemotherapies for metastatic urothelial tumors has allowed a significant decrease in toxicity, but no real improvement in terms of survival [3].

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Recent advances in the understanding of molecular biology have uncovered new tumoral markers, which represent potential targets for therapy. The human epidermal growth factor receptor-2 (HER 2) is currently one of the most investigated. HER 2 is overexpressed in various tumor types including breast, ovarian, endometrial, pancreatic, lung, and bladder cancer [4]. HER 2 is a membrane-bound receptor with tyrosine-kinase activity, and is implicated in oncogenic initiation and progression by interacting with the other members of the HER family to potentiate intracellular signaling [5]. In recent years, anti HER 2 monoclonal antibodies have been developed, and Trastuzumab (Herceptin^{TM}) was selected for clinical application [6]. Trastuzumab in combination with chemotherapy has been showed to improve survival of patients with metastatic breast cancer [7]. Some clinical trials evaluating the benefit of trastuzumab in other types of solid tumors, including urothelial cancer, are ongoing. In the current study, we report our preliminary experience with trastuzumab in six patients with metastatic transitional cell carcinoma of the urinary tract (5 patients with bladder cancer, and 1 with renal pelvic cancer).

2. Patients and methods

2.1. Patient selection

From november 2001 to august 2002, 17 patients from our institution received chemotherapy and/or palliative care for metastatic transitional cell carcinoma of the urinary tract. Of them, 9 were screened for HER 2 expression. Three patients showed a low HER 2 expression by immunochemistry. Therefore, they did not receive trastuzumab and were excluded from this study. The remaining 6 patients (66.7%) showed a high HER 2 expression. All these patients were treated with trastuzumab (Herceptin^{TM}) for a progressive disease, and are presented in the current study. The 6 patients had a normal renal function at the time of trastuzumab initiation.

This pilot study was not submitted to any ethical committee. The study preceeded a randomized multicentric phase II trial combining a platinum-based drug with or without trastuzumab, which is currently conducted in France by the GETUG (Groupe d'Etudes des Tumeurs Uro-Génitales). All patients had given an informed consent at the time of inclusion.

2.2. HER 2 expression analysis

HER 2 expression was determined using monoclonal antibody CB 11, either at the time of diagnosis or at the time of tumor progression when trastuzumab therapy was considered. A high HER 2 expression was defined as more than 90% of the tumoral cells showing strong staining intensity for HER 2 (score, 3+).

2.3. Patient treatment and follow-up

The patients received a weekly intravenous administration of trastuzumab (initial dose of 4 mg/kg, followed by 2 mg/kg for other courses). A total of 6 courses was given. In 4 patients (patients 1, 2, 3 and 5), trastuzumab was administered in combination with paclitaxel (175 mg/m^2) and carboplatin at an area under the curve (AUC) of 6. One patient (patient 4) received the same combination of trastuzumab and paclitaxel, but without carboplatin. The remaining patient (patient 6) received only trastuzumab.

All the patients had tumor measurement by pulmonary and abdominal CT scan and bone scintigraphy after cycle 3 and cycle 6 of therapy. The patient outcomes were prospectively collected. The regression of metastases was estimated using the RECIST criteria. Toxicities were graded according to the National Cancer Institute common toxicity criteria (version 2). Blood samples were collected weekly during each cycle, for blood count and assessment of renal and hepatic functions. An echocardiogram was performed at the end of each cycle to assess left ventricular function.

3. Results

3.1. Patient and tumor characteristics

Table 1 summarizes previous treatments and tumor characteristics at the time of trastuzumab initiation. Three patients with bladder cancer initially underwent radical cystectomy (patients 1, 2, and 4), and one with left renal pelvic cancer underwent nephroureterectomy (patient 6). Patients 1 and 4 experienced early pelvic recurrence after radical cystectomy, and then were treated with chemotherapy. Patient 1 received 4 courses

Table 1
Previous treatments and tumor characteristics at the time of trastuzumab initiation

Patients	Age (years)	Previous surgery	Previous chemotherapy and response	Lymph nodes	Metastases
1	58	Radical cystectomy	Gemcitabine + cisplatin (4 courses) PR[a] ~ 30%	None	Liver
2	65	Radical cystectomy	None	Bilateral, lomboaortic	Peritoneal carcinosis, Bone
3	60	None	None	Bilateral, iliac and lomboaortic	Bone
4	50	Radical cystectomy	MVAC[b] (6 courses) gemcitabine + oxaliplatin (4 courses) PR ~ 20%	Bilateral, iliac	Liver, lungs
5	51	None	Gemcitabine + cisplatin (3 courses) PR ~ 50%	None	Liver, lungs
6	60	Nephro ureterectomy	gemcitabine + cisplatin (6 courses) PR ~ 50%	None	Liver, retroperitoneal recurrence

[a] PR: partial regression.
[b] MVAC: Methotrexate, Vinblastin, Adriamycin, Cisplatin.