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Trastuzumab (Herceptin®) in patients with HER-2-overexpressing metastatic or locally advanced transitional cell carcinoma of the bladder: report on 7 patients

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Metastatic urothelial cancer is a rapidly fatal disease with a median survival of less than one year. Despite treatment with radical cystectomy in patients with advanced disease, approximatively 50–60% patients relapse with distant metastasic disease. Chemotherapy combining use of methotrexate, vinblastine, doxorubicin and cisplastin (M-VAC) has been considered to be the treatment of choice for patients with metastatic transitional cell carcinoma (TCC) of the bladder in many centers.[1] However, a number of recent regimens have been evaluated to improve efficacy and reduce toxicity of chemotherapy with encouraging results. A phase II study with the combination of carboplatin and paclitaxel reported a 72% objective response rate with mild to moderate toxicity in 32 patients suffering from advanced TCC.[2] More recently,the combination of cisplatin and gemcitabin has been shown to be an equally effective, but less toxic regimen in comparison to M-VAC in a large randomized study, establishing this treatment as a new standard of care in metastatic bladder cancer.[3]

ErbB-2 is an oncogene encoding a type 1 tyrosine kinase growth factor receptor; its overexpression has been found in urothelial tumors and shown to be associated with a poor prognosis in TCC of the bladder.[4] Trastuzumab (Herceptin) is a recombinant monoclonal antibody that selectively targets the extracellular domain of the epidermal growth factor receptor 2 protein. Numerous studies have examined the incidence and clinical significance of ErbB-2 amplifications and

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overexpression in TCC of the bladder. with a frequency of amplification ranging from 7%[5] to 17% and 26%, respectively.[6,7] In contrast to breast carcinoma, in bladder cancer 2+-positive cells (Hercept Test®, DAKO) do not show a gene amplification detectable by FISH.

The encouraging results obtained with the combination of carboplatin and paclitaxel in patients with TCC as well as the reported synergistic activity of Trastuzumab (Herceptin) and paclitaxel in breast cancer suggested that simultaneous use of these two compounds might be a potentially attractive treatment option in TCC of the bladder.

We tested the efficacy of Trastuzumab administered on a weekly schedule in seven patients (61–74 years of age) with histologically confirmed transitional cell carcinoma of the bladder. Patients were to have clinically or radiologically measurable or evaluable disease, ErbB-2 overexpression (3+ with HerceptTest®, DAKO), and a Karnofsky performance status $\geqslant$60%. Prior chemotherapy (adjuvant or/and palliative) was allowed. Patients received trastuzumab at 4 mg/kg i.v. as a loading dose on day 1 followed by 2 mg/kg infusions weekly. Efficacy parameters were objective response rate, time to progression, and overall survival. Safety and tolerability parameters were also determined.

Two patients were treatment-naive, all others had received prior chemotherapy, radiotherapy or both. Stable disease was observed in one patient (treatment-naive), he received study therapy for 19 weeks. All other patients suffered from progressive disease. Trastuzumab was generally well tolerated. Adverse events were mild to moderate for all patients except for one grade 4 toxicity, developing thrombosis with pulmonary embolism, and one with grade 3, suffering from fatigue.

It is still unclear if the tumor responses observed in bladder cancer patients translate into significant clinical benefit or improved survival,[8] but a review of all phase and III studies published in the English literature over the last 20 years indicates that there is some evidence that patients with extravesical diseases with lymph node involvement might benefit from neoadjuvant treatment with cisplatinum-based chemotherapy.

In our study, treatment with weekly trastuzumab in patients with transitional cell carcinoma of the bladder was safe and well tolerated. One out seven patients experienced stable disease for 19 weeks and side-effects were mostly mild to moderate.

In all other patients, progressive disease (PD) with fatal outcome was observed. There is, therefore, no evidence for efficacy of trastuzumab in patients with metastatic or advanced transitional cell carcinoma of the bladder in this limited patient pool. On one side, this low response to trastuzumab treatment could be due to a lack of gene amplification, and as a consequence, lower levels of gene expression as compared to breast cancer.[9] It has been shown in breast cancer that mostly tumors carrying an ErbB-2 amplification respond to the anti-ErbB2 therapy trastuzumab. A recent study demonstrated that in 75 patients with TCC, 97% had polysomy 17, 92% had an increased ErbB-2 copy number, and only 7% had an ErbB-2 gene amplification.[9] These findings suggest that only 4/75 (5%) of TCCs would be suitable for treatment with trastuzumab. On the other side, a further reason for the lack of efficacy could be the very far-advanced state of disease and short survival time of the patients and the rapidity of the metastatic progression. Other studies suggested that earlier treatment might be a more promising approach. In contrast to our results, a recent study reported the safety and efficacy of trastuzumab on six patients with metastatic TTC of the urinary tract all of which achieved a partial regression of 30–80%. However, six out of seven patients received concomitant chemotherapy, and thus, the results cannot necessarily be attributed to trastuzumab.[10] Efficacy of monotherapy with trastuzumab in metastatic breast cancer is modest as well, and it was the addition of chemotherapy, which made that drug an attractive treatment option. The same might be true in metastatic bladder cancer.

The statistical power of our study is rather low, due to the small number of recruited patients. Larger trials will be needed to determine if trastuzumab might become a therapeutic option in advanced bladder cancer.

Conflict of interest statement

None declared.

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