Publications

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Mini Review

Maintenance Trastuzumabplus Letrozoleafter Complete Response to Trastuzumab-Emtansine in A Patient with HER2-Positive, Hormone Receptor Positive Metastatic Breast Cancer

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1. Mini Review

Although metastatic breast cancer overexpressing Human Epidermal Growth Factor Receptor-2 (HER2) is a not curable disease, the introduction of HER2-targeted agents, including trastuzumab, pertuzumab, trastuzumab-emtansine and lapatinib, has significantly improved survival with a small proportion of patients experiencing durable complete remission [1-4]. Up to 5-10% of patients treated with HER2-targeted agents may achieve a complete response in the first-line setting [1,5] and, although more rarely, complete responses may be observed also in second line and beyond. Particularly, in the phase 3 Emilia study patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane were randomized to receive T-DM1 or lapatinib plus capecitabine, and complete response rates were 1% and 0.5% in the two arms, respectively [4]. For patients achieving complete response, there are currently no guidelines on the optimal duration of HER2-targeted therapy and the optimal management of these patients is controversial. Here we report the case of a patient with estrogen Receptor (ER) positive, Progesterone Receptor (PgR) positive, HER2-positive, metastatic breast cancer who achieved a complete response with T-DM1 and was therefore treated with maintenance therapy with trastuzumab plus letrozole.

In 2009, a 44–year-old female was diagnosed with Hormone Receptors (HR) positive, HER2-positive, IIA stage, right breast cancer. After right mastectomy and axillary lymph node dissection, she received adjuvant chemotherapy combined with 1-year trastuzumab and endocrine therapy with tamoxifen plus goserelin. At the time of completion of 1-year trastuzumab, abdominal ultrasound revealed liver metastases. Liver biopsy confirmed a metastatic HR-positive/HER2-positive breast cancer. In February 2011, she was enrolled in the MARIANNE study, a randomized phase 3 trial comparing T-DM1, T-DM1 plus pertuzumab, and trastuzumab plus taxane for patients with HER2-positive, metastatic breast cancer. Within this study, the patient was treated with T-DM1 achieving a radiologic complete response after 12 weeks of treatment, as documented by CT scan. FDG-PET/CT also showed a metabolic complete response. In February 2013, the patient chose to discontinue T-DM1. At that time, CT scan confirmed a persistent complete response and a repeated liver biopsy revealed pathological complete response of liver metastases. Therefore, we decided to start a maintenance therapy with letrozole plus trastuzumab. This treatment has been well tolerated, with no adverse events. Maintenance therapy is currently ongoing, and disease is still in complete remission.

In pivotal clinical trials, T-DM1 was generally continued until disease progression or unmanageable toxicity [4,6,7]. Our patient discontinued T-DM1 after 2 years of treatment and was then started on a maintenance therapy with trastuzumab plus letrozole, achieving prolonged complete remission. To our knowledge, this is the first report of trastuzumab-based maintenance therapy after complete response to T-DM1.

Among patients treated with trastuzumab-based therapy, prolonged remissions are predominantly seen in patients with HR-negative disease and liver metastases [8]. In this case, however,

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the patient had HR-positive/HER2-positive breast cancer, thus we started endocrine therapy in association with trastuzumab as maintenance treatment. The addition of endocrine therapy to trastuzumab is considered a reasonable strategy according to ESMO guidelines [9], although it has not been extensively investigated in randomized trials. Given the optimal tolerability of trastuzumab plus letrozole in this patient, we decided to continue with maintenance therapy and the patient has been receiving treatment for 5 years with no evidence of relapse.

In the maintenance setting, the optimal duration of trastuzumab in patients achieving a complete remission is unknown, and often oncologists continue trastuzumab indefinitely, although evidence on long-term safety of trastuzumab as well as evidence on risk of relapse after trastuzumab cessation is limited [10]. However, discontinuation of trastuzumab after several years of sustained complete remission may be reasonable in some patients, particularly if treatment re-challenge is available in case of progression. Some authors reported a sustained complete response after trastuzumab discontinuation. In a recent series, however, among 27 patients who discontinued trastuzumab after complete response, 4 patients experienced progressive disease [11]. Therefore, discontinuation of maintenance trastuzumab in this patient population after a limited time should be explored cautiously.

In conclusion, this case suggests that maintenance therapy with trastuzumab plus letrozole after complete response achieved with T-DM1 in patients with HR-positive/HER2-positive metastatic breast cancer may be feasible, well tolerated, and associated with prolonged remission. Therefore, we believe that this approach could be considered for selected patients. However, the optimal duration of maintenance therapy is still uncertain.

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