Trastuzumab as Single Agent Therapy for HER2-Positive Metastatic Breast Cancer

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Trastuzumab is an integral part of therapy for patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Its activity as a single agent was demonstrated in several phase II trials. One critical trial evaluated trastuzumab as a single agent in women with HER2-positive breast cancer who have not previously received chemotherapy for metastatic disease [1]. The response rate was 26%; and the clinical benefit rate was 38% in all assessable patients. The median survival was 24.4 months, which is comparable with the survival rate in the pivotal phase III combination trial of chemotherapy and trastuzumab which will be discussed below [2]. This trial demonstrated that single agent trastuzumab is active and an important treatment option in HER2-positive metastatic breast cancer.

Another large phase II trial indicated that trastuzumab monotherapy is active in HER2-positive metastatic breast cancer in women previously treated with chemotherapy for metastatic disease [3]. A total of 222 women with HER2-positive metastatic breast cancer that had progressed after one or two chemotherapy regimens were enrolled in this trial. The objective response rate was 15% (reviewed by an independent response evaluation committee) in the intent-to-treat population. The median duration of response was 9.1 months and the median duration of survival was 13 months.

In this issue of Onkologie Clemens et al. [4] present another report of the activity of single agent trastuzumab in patients with HER2-positive breast cancer who had previously received at least one chemotherapy regimen for metastatic disease. This report is of interest because it contains information gleaned from an expanded access trial before trastuzumab was made available in clinical practice in Germany. It contains data from 70 patients enrolled from 28 institutions across Germany during a one-year period in 1999–2000 and is therefore inclusive in scope. Eligibility criteria were relaxed with regard to extent of disease and previous types of therapy but a stringent definition of positive HER-2 as 3+ by immunohistochemistry or 2+ with a positive FISH assay was employed. Trastuzumab dose and schedule were standard. The overall response rate was 19% and disease stabilization was reported in an additional 29% of patients. Single agent trastuzumab was well tolerated. The most frequent adverse event was infusion-related syndrome, and symptomatic heart insufficiency of uncertain type was reported in 3 cases. Thus, in aggregate, this case series validates the efficacy and toxicity results of other trials of monotherapy with trastuzumab [3] although the frequency and type of cardiac events are more difficult to compare across different trials due to differences in definitions of a cardiac event.

This report also raises several directions for the future. A major question is the role of combination therapy with trastuzumab and other agents including chemotherapy or other targeted agents. The pivotal phase III trial of first-line trastuzumab with various chemotherapy regimens compared to chemotherapy alone demonstrated a significant improvement in survival (25.1 versus 20.3 months) and overall response (50 versus 32%) [2]. This study led to the approval of trastuzumab with paclitaxel for first-line treatment of HER2-positive metastatic breast cancer as well as the conduct of several trials of combination therapy in the adjuvant setting. Together these studies showed that addition of trastuzumab to adjuvant chemotherapy led to a 40% decrease in recurrence compared with chemotherapy alone [5]. Early results from one of these studies suggest that the combination of paclitaxel with trastuzumab gives improved outcomes over a sequence of paclitaxel followed by trastuzumab [6].

It is noteworthy that Clemens et al. report that 8 patients had newly diagnosed central nervous system (CNS) lesions at the time of detection of progressive disease. As demonstrated in this trial and others, trastuzumab improves outcomes in patients with HER2-positive breast cancer, but the CNS remains an important site of initial and subsequent relapse. Other targeted therapies, such as lapatinib have demonstrated activity for CNS metastases [7, 8]. In a phase III study evaluating capecitabine versus capecitabine plus lapatinib in women with HER2-positive metastatic breast cancer, the addition of lapatinib led to an improvement in outcomes and numerically fewer patients with symptomatic CNS progression as part of their first progression event [9, 10]. New treatment ap-
proaches are important for patients with CNS involvement, particularly for patients with HER2-positive breast cancer.

The results of the pivotal phase III trial that investigated the addition of lapatinib to capecitabine in patients with HER2-positive advanced breast cancer [9, 10] led to the US Food and Drug Administration’s approval of lapatinib in combination with capecitabine for the treatment of patients with metastatic HER2-positive breast cancer that progressed after trastuzumab, anthracyclines, and taxanes. Lapatinib in combination with trastuzumab has demonstrated an improvement in overall survival compared to lapatinib alone in patients who have progressed on prior trastuzumab-containing regimens for metastatic breast cancer [11]. This study confirms a role for combined HER2 blockade. This study also demonstrates that lapatinib in combination with trastuzumab offers a chemotherapy-free option.

Other novel agents have also been evaluated in combination with trastuzumab. A phase II study of pertuzumab in combination with trastuzumab demonstrated an ORR of 24.2% in patients with metastatic breast cancer progressing after prior trastuzumab therapy [12]. This trial showed that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with metastatic HER2-positive breast cancer who have progressed during prior trastuzumab therapy.

Studies are also evaluating trastuzumab-MCC-DM1 (T-DM1), a conjugate of trastuzumab with the cytotoxic maytansine. A phase III trial is currently evaluating T-DM1 in comparison with the combination of capecitabine and lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy [13]. Finally, simultaneous targeting of multiple growth factor pathways is also a strategy of interest. Initial support for this approach comes from a phase II study demonstrating that the combination of trastuzumab and bevacizumab has a clinical response rate of 48% as first-line therapy in metastatic HER2-positive breast cancer [14].

In the results reported by Clemens et al. are a confirming validation of findings from another large phase II trial [3]. Together these trials demonstrate that single agent trastuzumab may be an option as treatment for HER2-positive metastatic breast cancer. Today trastuzumab is the foundation of treatment for women with HER2-positive disease in early stage breast cancer and it seems likely that continued development of targeted novel agents like trastuzumab will give hope for the future [15].

Conflicts of Interest

The authors did not declare any conflict of interest.

References


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Onkologic 2010;33:420–421