Review Article

Perspective of Trastuzumab Treatment

Hiroji Iwata

Department of Breast Oncology, Aichi Cancer Center Hospital, Japan

Trastuzumab (Herceptin®) has many benefits for metastatic breast cancer patients with HER2 overexpression/amplification. Trastuzumab alone or trastuzumab in combination with chemotherapy regimens are standard treatment worldwide as first line therapy for metastatic breast cancer patients with HER2 overexpression/amplification. Furthermore, an international collaboration for adjuvant trastuzumab trials showed last year that trastuzumab treatment improves disease-free and overall survival after or in combination with adjuvant chemotherapy. However, there are many uncertain issues concerning trastuzumab adjuvant and metastatic treatment, such as treatment beyond disease progression (PD), combination with hormone therapy, duration of adjuvant treatment, and cardiac safety of long term treatment.


Key words: Trastuzumab, Metastatic breast cancer, (neo) Adjuvant treatment, Cardiac toxicity

Introduction

HER2/neu (hereinafter HER2) belongs to a family of four transmembrane tyrosine kinase receptors that mediate cell growth, differentiation, and survival1. HER2 overexpression/amplification occurs in approximately 15 to 25% of human breast cancer patients, and is associated with a more aggressive natural history2. Trastuzumab (Herceptin®), a humanized monoclonal antibody targeted to the extracellular domain of HER2, benefits patients with metastatic breast cancer3,4, and improves disease-free survival (DFS) and overall survival (OS) after adjuvant chemotherapy5, and in combination with chemotherapy6. This paper describes up to date findings and the current perspective of trastuzumab treatment.

Trastuzumab treatment is the standard therapy worldwide for metastatic and advanced breast cancer with HER2 overexpression. Initial treatment with trastuzumab has shown prolonged overall survival as a first-line therapy for metastatic breast cancer patients7. Therefore, we should use trastuzumab with or without chemotherapy for the first-line treatment of metastatic breast cancer patients. Many Japanese investigators think that the treatment strategy for metastatic breast cancer depends on Hortobagy's algorithm8. If a patient's condition is non-life threatening, investigators will select a mild treatment such as hormonal therapy for the initial therapy. Which treatment do you chose between trastuzumab monotherapy and trastuzumab in combination with chemotherapy as initial therapy for non-life threatening metastatic breast cancer with HER2 overexpression? I recommend the combination treatment with chemotherapy, because its response rate is much higher than that for trastuzumab monotherapy. The response rate of combination treatment and monotherapy has been shown to be 60 to 70%9,10 and 20 to 30%8,11, respectively, in many studies.

When should trastuzumab treatment be stopped or continued beyond the determination of
progressive disease (PD) for the combination treatment with trastuzumab and chemotherapy? This issue is uncertain, because there is no prospective data evidence about this question, although there are some experimental and retrospective data. However, a randomized clinical trial is presently ongoing in the world comparing the efficacy of capecitabine monotherapy and trastuzumab with capecitabine for patients previously treated with trastuzumab with taxane.

**Adjuvant Treatment**

Adjuvant trastuzumab treatment improves DFS and OS for early breast cancer patients, based on data from four large trials\(^5,6,11)\) and one small trial\(^12)\) (Fig 1). There are several differences in trial design and data of adverse events among the trials (Table 1, 2)\(^5,6,11,13)\). Characteristics of these five trials are outlined below.

1) Trastuzumab was administered as sequential usage after any chemotherapies in the Herceptin adjuvant (HERA) trial. But trastuzumab was administered as concurrent usage therapy with taxanes in the other four trials.

2) Trastuzumab was scheduled as tri-weekly and weekly treatment in the HERA trial and other four trials, respectively.

---

**Fig 1.** Adjuvant Trastuzumab study design.

**Table 1. Schedule of Adjuvant Trastuzumab Study**

<table>
<thead>
<tr>
<th>NSABP + NCCTG</th>
<th>HERA</th>
<th>BCIRG006</th>
<th>FinHer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy regimen</td>
<td>AC followed by Paclitaxel (weekly or q3W)</td>
<td>All standard chemotherapy</td>
<td>AC followed by Docetaxel</td>
</tr>
<tr>
<td>trastuzumab</td>
<td>concurrent or sequential</td>
<td>sequential</td>
<td>concurrent</td>
</tr>
<tr>
<td>T schedule</td>
<td>Weekly</td>
<td>q3W</td>
<td>Weekly</td>
</tr>
<tr>
<td>times</td>
<td>52 times</td>
<td>1Y or 2Y</td>
<td>52 times</td>
</tr>
<tr>
<td>n</td>
<td>positive</td>
<td>positive or negative high risk</td>
<td>positive or negative high risk</td>
</tr>
<tr>
<td>Median follow up</td>
<td>24M</td>
<td>12M</td>
<td>23M</td>
</tr>
</tbody>
</table>

---

**Notes:**
- Pac: Paclitaxel, Doc: Docetaxel, H: Trastuzumab, CT: Chemotherapy
- Table 1 shows the schedule of adjuvant trastuzumab study, including the groups NSABP + NCCTG, HERA, BCIRG006, and FinHer.
- The table outlines the total numbers, chemotherapy regimen, trastuzumab usage, T schedule, and median follow-up time for each group.

---

**Breast Cancer Vol. 14 No. 2 April 2007**

- NSABP B-31
- NCCTG
- HERA
- BCIRG006
- Table 1: Schedule of Adjuvant Trastuzumab Study

---

**Key Points:**
- Adjuvant trastuzumab improves DFS and OS in early breast cancer patients.
- There are variations in trial design and adverse events among different studies.
- A randomized clinical trial is ongoing to compare the efficacy of trastuzumab with taxanes versus capecitabine.

---

**Additional Information:**
- The image includes a diagram and textual content related to adjuvant trastuzumab treatments.