20.1 Introduction

Up to 25% of women with breast cancer have tumors, which are human epidermal growth factor receptor-2 (HER2) positive, associated with an aggressive phenotype, higher recurrence rate and reduced survival [1, 2]. In these patients with poorer prognosis, combination chemotherapy (+endocrine therapy), up until recently, was the only treatment modality available.

Trastuzumab (Herceptin®), a monoclonal antibody directed against the extracellular domain of HER2, has been investigated extensively in the clinical setting of advanced breast cancer, both as monotherapy and in combination with standard chemotherapeutic drugs. More recently, it has been tested in HER2-positive patients with early breast cancer in five adjuvant trials.

Despite impressive results in both clinical arenas, many controversies remain regarding its use. For patients with early breast cancer, controversy still exists regarding the optimum timing, duration, and schedule of trastuzumab. For those with metastatic disease, the controversy of whether to cease altogether or continue with trastuzumab beyond progression still needs answering.

This chapter discusses the evolution of HER2-targeted therapy, beginning with the initial success of trastuzumab to the controversies that remain, and from there, to the discussion of newer anti-HER2 approaches currently under investigation.

20.2 Targeting the HER2 Receptor

HER2 belongs to the human epidermal growth factor receptor (EGFR) family of tyrosine kinases consisting of EGFR (HER1; erbB1), HER2 (erbB2, HER2/neu), HER3 (erbB3), and HER4 (erbB4). All these receptors have an extracellular ligand-binding region, a single membrane-spanning region, and a cytoplasmic tyrosine-kinase-containing domain, the last being absent in HER3. Ligand binding to the extracellular region results in homo- and heterodimer activation of the cytoplasmic kinase domain and phosphorylation of a specific tyrosine [3], leading to the activation of various intracellular signaling pathways involved in cell proliferation and survival.

HER2 was first identified as an oncogene activated by a point mutation in chemically-induced rat neuroblastomas [4], and soon after, found to be amplified in breast cancer cell lines [5]. In the clinic, patients with HER2 gene-amplified tumors were shown to represent approximately 25–30% of the human breast population, having poorer disease-free survival (DFS) [6–8], and also displaying resistance to certain chemotherapeutic agents [9–11].

With the accumulating body of evidence supporting the HER2 oncogene hypothesis, the HER2 receptor represented an ideal target for anticancer therapy. By targeting HER2 receptors, either intracellularly or extracellularly, downstream pathways could be indirectly inhibited to induce cell cycle arrest, apoptosis, as well as inhibition of tumor cell invasion and metastases [12].

Two main therapeutic strategies have been developed so far to target the HER2 receptor; monoclonal antibodies, and small molecule kinase inhibitors. Trastuzumab (Herceptin; Genentech, South San Francisco) is a recombinant, humanized anti-HER2 monoclonal antibody and was the first clinically active anti-HER2 therapy to be characterized. Trastuzumab exerts its action...
through several mechanisms including (1) induction of receptor downregulation/degradation [13], (2) prevention of HER2 ectodomain cleavage [14], (3) inhibition of HER2 kinase signal transduction [15] via ADCC, and (4) inhibition of angiogenesis [16].

On the other hand, small molecule HER2 kinase inhibitors are cheaper to produce but are often less specific, since they can simultaneously inhibit multiple targets. Unlike trastuzumab, most of them are still in a relatively early phase of clinical development.

20.2.1 Importance of Accurately Identifying HER2

A HER2 positive status is not only an adverse prognostic marker in breast cancer but also a positive predictive marker of response to anti-HER2 therapies. Tailored treatment requires proper identification of these patients who are most likely to derive benefit, and least likely to experience unnecessary toxicity. The guidelines from the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) for HER2 testing have recently been published, endeavoring to improve laboratory standardization and test reproducibility.

HER2 status is thus reported as an algorithm of positive, equivocal, and negative results defined as (a) HER2 positive – immunohistochemistry (IHC) staining of 3+ (uniform, intense membrane staining of >30% of invasive tumor cells, a fluorescence in situ hybridization (FISH) result of more than 6.0 HER2 gene copies per nucleus, or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; (b) HER2 negative – IHC staining of 0 or 1+ FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8; and (c) HER2 equivocal – IHC 3+ staining of 30% or less of invasive tumor cells or 2+ staining, a FISH result of 4–6 HER2 gene copies per nucleus, or FISH ratio between 1.8 and 2.2.

20.3 Trastuzumab in the Metastatic Setting

Since the first reports of trastuzumab’s activity in HER2+ MBC, many studies have been conducted to investigate the optimum schedule in this patient group, both as single-agent therapy and in combination.

20.3.1 Single-agent Therapy in Heavily Pretreated Patients

In an early trial evaluating weekly trastuzumab efficacy in 222 women with HER2+ MBC that had progressed after one or two chemotherapy regimens [17], the response rate (RR) was 15% in the intent-to-treat population and was significantly higher in strong HER2+ overexpressors (18 vs. 6% for those with 3+ and 2+ IHC, respectively). The median response duration was 9.1 months. Cardiac dysfunction was the most common adverse event, occurring in 5% of treated patients, many of whom had received prior doxorubicin.

The alternative 3-weekly schedule of trastuzumab was investigated in a phase II study [18] of 105 patients where comparable results were achieved (overall RR of 19% and clinical benefit rate of 33%). Median time to progression (TTP) was 3.4 months (range 0.6–23.6 months).

20.3.2 First-Line Single-Agent Therapy

The benefit of first-line trastuzumab monotherapy was studied in 114 women with HER2+ MBC [19], randomized to receive first-line treatment with trastuzumab 4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4 mg/kg weekly. RRs in 111 assessable patients with 3+ and 2+ HER2 overexpression by IHC were 35% (95% CI 24.4–44.7%) and none (95% CI, 0–15.5%), respectively. The RRs in 108 assessable patients with and without HER2 gene amplification by FISH analysis were 34% (95% CI 23.9–45.7%) and 7% (95% CI 0.8–22.8%), respectively. Interestingly, overall RR was nearly double that reported for previously treated patients. There was no clear evidence of a dose-response relationship for response, survival, or adverse events.

20.3.3 Trastuzumab in Combination with Chemotherapy

20.3.3.1 Trastuzumab and Taxanes

Preclinical studies have shown additive or synergistic interactions between trastuzumab and multiple cytotoxic agents, including platinum analogs, taxanes,