Symposium article

Proposed treatment guidelines for HER2-positive metastatic breast cancer in Europe

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Summary

The human epidermal growth factor receptor-2 (HER2) is overexpressed/amplified in 20%-30% of human breast tumors and is a marker for a poor prognosis. For these reasons, HER2 has been selected as a therapeutic target for breast cancer treatment. Oncologists can no longer ignore the importance of HER2 status for treatment algorithms in breast cancer. In light of the consequences of HER2 status on treatment selection, further research is warranted to refine and standardize HER2 testing in order to minimize false-negative results and optimize selection of treatment pathways. The anti-HER2 monoclonal antibody (MAb) trastuzumab (Herceptin) has proven valuable in treating HER2-positive, advanced-disease patients, and the availability of this novel biologic agent has important implications for clinical practice. This review describes a set of guidelines based on the current options for treatment of breast cancer. Two important factors have been taken into account in compiling these recommendations: (1) the lack of level I evidence to convincingly demonstrate the value of HER2 as a predictive marker for resistance or sensitivity to chemo- and hormonal therapy, and (2) the recently published pivotal phase II and III trial data proving the efficacy of trastuzumab as a single agent and in combination with chemotherapy in HER2-positive metastatic breast cancer.

Key words: anti-HER2 monoclonal antibody, HER2, Herceptin, predictive marker, prognostic marker, trastuzumab, treatment guidelines

Introduction

It is predicted that no further significant improvements in the survival of women with metastatic breast cancer are likely to result from the use of traditional chemo-therapeutic agents, even in modified treatment regimens or combinations of the existing agents. The severe and often debilitating side effects accompanying chemotherapy also present an obstacle to the use of many cytotoxic agents [1]. Thus, there is an urgent need for novel treatment approaches that provide improved patient outcomes.

The advances in drug development for breast cancer therapy over the past few decades have provided oncologists with a broader choice of treatments to offer patients with metastatic disease. In particular there has been increased emphasis on improved symptom control and quality of life, and a growing trend towards enhancing treatment individualization. Indeed, an area of active interest is the growing search for novel tumor or serum markers that may be of predictive significance for the individual patient.

In addition to the powerful cytotoxic drugs, paclitaxel and docetaxel, which were introduced in the early 1990s, and other novel drug families such as the anti-metabolites and topoisoamerase I inhibitors, considerable research efforts have been devoted to the development of new biologic therapies that specifically target the tyrosine kinase receptor-mediated signal transduction pathway. One such target is the human epidermal growth factor receptor-2 (HER2). HER2 is a tyrosine kinase membrane receptor [2] that, on activation, induces a phosphorylation cascade in cytoplasmic kinases (including ras and raf), leading to increased protein transcription and cellular growth [3]. A large amount of evidence has emerged to show that HER2 plays a central role in oncogenic transformation and tumorigenesis by interacting with the other members of the HER family to potentiate intracellular signaling [4-6].

HER2 plays a pivotal role in the biology of breast cancer. The HER2 proto-oncogene is overexpressed/amplified in 20%-30% of breast cancers and HER2-positive tumors usually show more aggressive behavior [7, 8]. Of particular clinical significance is that overexpression/amplification of HER2 has been reported to be an independent prognostic factor in breast cancer patients [7, 8]. The involvement of the HER2 receptor in the pathogenesis of breast cancer and the link between HER2-positive status and poor prognosis first reported by Slamon and colleagues has been substantiated by numerous studies [9-16]. The occurrence of HER2 protein levels that are several orders of magnitude greater on the cell surface of HER2-positive cells compared with adjacent normal breast epithelium [12, 17, 18], combined
with the value of HER2 as a molecular marker to predict a reduced disease-free and overall survival, make this receptor an important potential therapeutic target in breast cancer.

The potential impact of HER2 status on the planning of individualized treatment underscores the need to refine and standardize HER2 testing in order to minimize false-negative results. Currently, HER2 testing results are influenced by numerous factors, including the methods employed to determine HER2 status, as well as the antibodies and scoring systems used. Clearly, well-standardized assay systems and quality-control programs to assess whether individual laboratories can perform HER2 testing and scoring accurately and reproducibly are required.

**A novel treatment for HER2-positive patients**

An increased understanding of the biology of breast cancer over the past 30 years has led to the identification of a number of novel therapeutic approaches to anti-cancer treatment. In particular, the targeting properties of the immune system offer an approach to improve the selectivity of anti-cancer therapies. The humanized anti-HER2 monoclonal antibody (MAb) trastuzumab (Herceptin), which targets HER2 and activates the immune system to block the physiologic function of the HER2-signaling network [19], has been shown to have significant therapeutic value in HER2-positive metastatic breast cancer patients [20–23]. A phase II pivotal trial of 222 patients who had received extensive prior chemotherapy for metastatic disease indicated that trastuzumab monotherapy yielded a 15% response rate with a median duration of nine months [20]. Moreover, in a pivotal phase III trial of 469 patients, first-line therapy consisting of trastuzumab plus chemotherapy provided an approximate 25% increase in median survival in metastatic breast cancer patients compared with chemotherapy alone [21–23]. In both trials, trastuzumab was well tolerated with the only severe adverse effect being cardiac toxicity, which was, in most cases, transient and manageable.

The availability of new anti-cancer agents such as anti-HER2 MAbs means that clinicians now face the challenge of where and how to integrate novel biologic therapies into existing treatment algorithms. The emergence of the oncogene-targeted therapy, trastuzumab, has special impact on the treatment options available to HER2-positive breast cancer patients.

**Factors influencing treatment guidelines**

Another difficulty confronting clinicians is that the available data influencing the choice of therapy are by no means complete and are subject to change. In the provision of the treatment guidelines presented here, a number of important considerations have been taken into account. The first of these relates to the continued controversy surrounding the potential predictive value of HER2 with respect to response to classical forms of breast cancer therapy. Fundamentally, there is a distinct lack of level I evidence (defined as evidence obtained from meta-analysis of multiple, well-designed, controlled studies or from high-power randomized, controlled clinical trials) to convincingly demonstrate the value of HER2 as a predictive marker for response to hormonal therapy or chemotherapy. The guidelines presented here are, therefore, based on current and still limited understanding of the implications of HER2 overexpression/amplification in breast cancer. Compared with the prognostic studies, the reports of therapy response prediction are fewer, involve smaller patient groups and have been generally less well controlled. Thus, while the data indicate that a HER2-positive status may correlate with increased resistance to certain hormone and/or chemotherapeutic agents, they do not enable any definitive conclusions to be made.

A number of studies have indicated that HER2 may be a marker of reduced response to hormonal therapy in breast cancer [24–27]. Some reports have indicated that HER2-positive patients may be resistant to therapy with tamoxifen [28–32]. However, other studies have revealed no predictive value of HER2 with respect to hormonal therapy [33–36].

The available data to implicate HER2 in response to chemotherapy are even less convincing and are derived mainly from adjuvant studies [9, 37]. Studies on the predictive value of HER2 status in determining response to anthracycline-based chemotherapy have also yielded conflicting conclusions [38–43]. Of these, the Southwest Oncology Group (SWOG) 8814 trial results reported by Ravdin and colleagues [44] showed that there was no statistically significant benefit of chemoendocrine (tamoxifen + CAF [cyclophosphamide, doxorubicin, 5-fluorouracil (5-FU)]) vs. tamoxifen alone in HER2-negative patients, but that chemoendocrine therapy appeared to be superior to tamoxifen in HER2-positive patients. Another study demonstrated that anthracycline-based therapy was significantly more effective in HER2-positive compared with HER2-negative patients [45]. While these studies suggest that HER2 overexpression is of possible value in selecting patients who may particularly benefit from anthracycline-based therapy, all studies have inherent weaknesses, including their retrospective nature, incomplete retrieval of tumor blocks and lack of standardization of HER2 evaluation. This means that the results should be interpreted with caution.

A major consideration in establishing where and how trastuzumab may fit into the current treatment guidelines for HER2-positive women are the phase II and III pivotal trial data of trastuzumab as a single agent and in combination with chemotherapy [20–23]. As second/third-line monotherapy, trastuzumab provided durable tumor responses and was well tolerated [20]. When administered with chemotherapy (anthracyclines or paclitaxel) as first-line therapy in a pivotal phase III
trial, trastuzumab produced an approximate 25% increase in the median survival of HER2-positive metastatic breast cancer patients [21-23]. The safety data collected in both pivotal trials indicate that trastuzumab achieves selective therapeutic effects without the often severe toxicity caused by chemotherapy. This favorable safety profile has obvious implications on the individualization of patient treatments with respect to quality of life.

Assessing prognosis and selecting treatment

The first step to developing a systemic treatment plan for a patient with metastatic disease is to perform a risk evaluation (Figure 1). This involves assessing the extent of metastatic disease and determining whether there are sites of disease that require urgent treatment. The next question for the clinician to ask is whether the patient is likely to benefit from hormonal therapy. Key factors in deciding on whether to opt for hormonal therapy are hormone-receptor status, the length of disease-free interval and location of metastatic disease.

Low risk

If the patient falls into the low-risk category, characterized by positive hormone receptors, long disease-free interval (more than two years), a limited number of metastases, soft tissue, bone metastases, and no major involvement of vital organs, the preferred treatment option is endocrine therapy. It is felt that, whenever possible, hormonal therapy should be administered until resistance develops. In view of the relative weakness and conflicting nature of the current data on the effects of HER2 and the effectiveness of therapy with tamoxifen, it seems unwise to deny estrogen-receptor (ER)-positive, HER2-expressing patients the possible benefits offered by endocrine therapy. However, given the possible limited value of hormonal agents when HER2 is co-expressed with ER or progesterone receptors (PgR) [24, 25, 27], it is important to follow patient progress closely. If the patient has a disease that cannot be followed reliably, then this option should probably be disregarded, bearing in mind that time to disease progression for HER2-positive patients receiving endocrine therapy might be less than six months [46].

At the time endocrine resistance develops, the clinician switches to chemotherapy. In cases where the HER2-positive patient still has indolent disease and is concerned about the side effects associated with chemotherapy, it may be reasonable to provide single-agent trastuzumab. This recommendation is supported by the benefits of single-agent trastuzumab in HER2-positive metastatic breast cancer patients observed in a pivotal phase II trial [20]. There are also promising data emerging from a phase II dose-response study of single-agent trastuzumab as first-line treatment in HER2-positive metastatic breast cancer patients without prior chemotherapy for stage IV disease [47]. In this trial, patients whose tumors are strongly HER2-positive (3+ by immunohistochemistry) achieve a response rate of 35%. For this reason, a high priority for clinical investigation is a randomized trial comparing first-line trastuzumab as a single agent followed by chemotherapy at the time of progression with first-line trastuzumab combined with chemotherapy. If the former strategy does not compromise survival benefit, it has the advantage of delaying chemotherapy by several months in responding patients.

Moderate or high risk

If evaluation of the patient reveals a moderate or high risk, characterized by negative hormone receptors, short disease-free interval (less than two years), extensive and/or visceral metastases, and vital organ involvement but no major organ dysfunction, chemotherapy is indicated. Knowledge of HER2 status and subgroup (i.e., IHC 1+, 2+ or 3+) is essential in the context of choosing whether to provide trastuzumab therapy; so far, benefit has been demonstrated for the HER2-positive 2+ and 3+ population as a whole, with subset analyses suggesting that the 3+ subgroup derives the greatest benefit.

Treatment preferences are also influenced by the type of therapy administered in the adjuvant setting. In the case of previous anthracycline exposure, which applies to many patients nowadays, the current best option appears to be the combination of trastuzumab with a taxane. The pivotal phase III trial data support the use of paclitaxel with trastuzumab: addition of trastuzumab to paclitaxel significantly increased survival, and improved the response rate from 17% to 41% and median response duration from 4.5 to 10.5 months, compared with paclitaxel alone. To assess the efficacy of trastuzumab with a taxane other than paclitaxel, a phase II trial of trastuzumab plus docetaxel as first-line therapy in HER2-positive metastatic breast cancer patients is underway and results are expected in 2001.

In the absence of prior anthracycline exposure, which

Figure 1. Proposed pattern of systemic management in metastatic breast cancer patients. [Updated from ASCO Educational Book 1999]
is uncommon today, the best treatment sequence remains to be defined. The first option is doxorubicin-cyclophosphamide (AC) followed, at progression, by taxane plus trastuzumab. This option is considered to be the conservative route. Although all the published studies suggest that, with adequate anthracycline doses, HER2-positive patients do relatively well with anthracycline-based treatment [44, 45, 48, 49], there may be some problems with delaying the use of trastuzumab until the time of progression. Firstly, the survival advantage seen in the phase III pivotal trial was associated with the use of trastuzumab upfront [22, 23]. Secondly, delaying the use of trastuzumab after prior AC may not be optimal, given the potential increased risk for cardiotoxicity. In the phase III combination trial, a higher incidence of cardiac dysfunction was observed in the trastuzumab plus AC group. In addition, the potentially short interval between AC and taxane plus trastuzumab in the conservative route calls for stringent cardiac monitoring.

The preferred route might be taxane plus trastuzumab used initially, which can be followed by anthracyclines at the time of progression. This approach is worth exploring as a strategy potentially associated with a reduced cardiac risk and offering the clear advantage of early trastuzumab use. If the data from recently closed phase III trials show anthracycline/taxane regimens to be associated with survival prolongation compared with AC, then the sequence AT (doxorubicin plus taxane) followed by trastuzumab at the time of progression would need to be tested.

In any event, the relatively poor prognosis of HER2-positive patients should motivate their clinicians to offer them participation in prospective clinical trials, which will explore a number of important issues, including the potential value of other trastuzumab-chemotherapy combinations, e.g., vinorelbine/5-FU ± trastuzumab, cyclophosphamide/methotrexate/5-FU ± trastuzumab. The results of ongoing phase II/III trials are eagerly awaited.

Treatment guidelines can change rapidly

The recommendations presented in Figure 1 have been updated since we last published guidelines for integration of new therapies into the breast cancer treatment algorithm [1]. In this context, it is important to appreciate that treatment guidelines can change completely within as little as six months. The positive results from the pivotal phase II and III trials have prompted numerous trials of trastuzumab either alone or in combination with chemotherapy. A phase II study has been conducted of weekly trastuzumab plus paclitaxel in HER2-positive and -negative patients with metastatic breast cancer [50]. A phase II study is underway to assess the safety and efficacy of trastuzumab in combination with vinorelbine as second- or third-line therapy for HER2-positive, metastatic breast cancer [51]. A relatively small phase II study is ongoing to investigate the combination of trastuzumab plus docetaxel in HER2-positive patients with metastatic breast cancer [52]. Future trials are expected to include trastuzumab in combination with other single agents such as docetaxel and aromatase inhibitors, and a trial to compare cardiotoxicity associated with epirubicin/cyclophosphamide (EC) plus trastuzumab (in HER2-positive patients) vs. EC alone (in HER2-negative patients). The accumulation of new trial data will lead to the expansion and likely revision of the treatment guidelines presented here. In addition, some guidelines should be accepted with caution as recommendations for certain treatment options await additional data from clinical trials regarding safety and/or efficacy.

Conclusions

The evidence to support HER2 as an important biologic marker in metastatic breast cancer, and the availability of a new and effective therapy targeting HER2, means that oncologists should view HER2 status as an important factor when choosing treatment programs for breast cancer patients. Despite the recognized significance of the HER2 receptor in the pathogenesis and prognosis of breast cancer, there is a need to standardize testing methods in order to provide accurate and reproducible testing results. The anti-HER2 MAb trastuzumab offers clear therapeutic benefits to HER2-positive patients. The reported activity and safety of trastuzumab, both alone and in combination with non-anthracycline-based chemotherapy, have important implications for current treatment guidelines. This novel biologic agent represents an attractive therapeutic option on account of its significant survival benefit in combination with chemotherapy. The available data indicate that trastuzumab is most beneficial when used initially; delaying the use of trastuzumab may preclude the survival benefits observed in the phase III clinical trial. Further exploration of the potential therapeutic efficacy of anti-HER2 MABs in combination with a variety of new and classic anti-cancer agents is likely to further improve outcomes in metastatic breast cancer, thereby influencing the treatment algorithms governing the management of breast cancer.

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