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Trastuzumab can be beneficial when used alone or with cytotoxic antitumor agents in selected patients with breast cancer.

Trastuzumab Use in Breast Cancer: Clinical Issues

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Background: Overexpression of the epidermal growth factor 2 HER2 in breast cancer tissue is associated with shorter survival. Trastuzumab, a monoclonal antibody against HER2, can induce tumor responses when given alone and enhances the effectiveness of several chemotherapeutic agents.

Methods: The recent clinical data on outcomes regarding testing for HER2 overexpression and the tolerance, toxicity, and antitumor effects of trastuzumab are reviewed.

Results: Trastuzumab use is indicated either alone or with chemotherapy only in patients with IHC 3+ or FISH+ test results and survival is prolonged in patients with metastatic disease. Cardiac toxicity differs from anthracycline cardiac toxicity and is often reversible.

Conclusions: The safety and efficacy profile of trastuzumab in patients with metastatic disease has led to large-scale testing of addition of the intervention in the adjuvant setting.

Introduction

The human epidermal growth factor receptor 2 (HER2), also known as *c-erbB-2* and *HER2/neu*, promotes cell growth and tumor development. HER2 protein overexpression is observed in 25% to 30% of primary breast cancers and is associated with shorter survival.¹

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to the

extracellular domain of HER2. In patients with metastatic breast carcinomas that overexpress HER2, trastuzumab produces antitumor responses when used alone.^{2,3} When combined with chemotherapy, response rates are increased, and survival is prolonged in comparison with treatment using chemotherapy alone.⁴ Trastuzumab was approved for use in the United States in 1998 and is now an integral part of the management of HER2-positive patients with metastatic breast cancer. Clinical studies to determine the role of trastuzumab in the adjuvant therapy of breast cancer patients who are at risk for recurrence are underway. The drug is generally well tolerated, but cardiac toxicity with trastuzumab has been reported in the range of 4% when the drug is used alone, with higher rates when used with chemotherapy.⁴

The extent of benefit from using the drug in association with chemotherapy in patients with HER2-positive advanced breast cancer is clear-cut. Slamon et al⁴ described near doubling of response rates and time to

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progression when trastuzumab was added to chemotherapy (doxorubicin/cyclophosphamide or paclitaxel) (Table 1). More important, a 5-month longer median overall survival was observed with the drug combination.

Several clinical questions concerning the optimal use of trastuzumab remain unanswered. Unfortunately, not all will be answered by clinical trials, in part because of a relative paucity of patients available who can be entered onto clinical research studies. This review is intended to identify some of the salient areas of controversy or lack of knowledge regarding the clinical use of trastuzumab in patients with breast cancer and to present available data that might assist clinicians in developing a rational approach to optimal clinical care of patients with HER2-overexpressing breast cancer.

Testing

The test used for determining HER2 protein expression in the trial by Slamon and colleagues⁴ is an immunohistochemical (IHC) “clinical trial assay” that is not commercially available. Several other IHC tests are commercially available, such as the HercepTest (Dako

Corp, Carpinteria, Calif). These usually report test results as 0, 1+, 2+, or 3+, with 3+ representing positive, 2+ indeterminate, and 0 or 1+ negative for HER2 protein expression. IHC tests performed in laboratories with a low testing volume were recently shown to correlate poorly with results from large-volume reference laboratories, a factor of particular concern to patients being accrued onto adjuvant treatment studies (Table 2).^{5,6} More recent follow-up suggests that correlations are now closer (E. Perez, MD, personal communication, September 2002).

Some laboratories now use quantitative image IHC analysis that provide reports of tumor HER2 protein overexpression as follows:

- Favorable (staining intensity in tumor cells <1.7)
- Unfavorable (staining intensity >2.4)
- Indeterminate (staining intensity between 1.7 and 2.3)

Trastuzumab therapy is considered for breast cancer patients with tumors that demonstrate 3+ overexpression or are in the “unfavorable” IHC category.

Fluorescence in situ hybridization (FISH) technology measures the extent of HER2 gene expression. The PathVysion (Vysis Inc, Downers Grove, Ill) HER2 DNA probe is considered positive when the ratio of HER2 to CEP 17 (chromosome enumeration probe) is ≥ 2 .⁷ FISH testing is probably the “gold standard” evaluation of HER2 activity and provides the best correlation with clinical response to trastuzumab,^{8,9} although results are similar when correlations of outcomes are made with IHC 3+ or IHC “unfavorable” test results. A FISH test is indicated in situations such as when an IHC result is reported as 2+ or indeterminate, or where there is an aggressive clinical picture of breast cancer in the face of an IHC report of 0 or 1+. Trastuzumab

Table 2. — HER2 Retesting at Control Reference Lab (Lab Corp)

	Initial Submitted Result	Central HercepTest Not 3+	Central PathVysion FISH Negative	Both Central Assays Negative
Initial Test Done at Small-Volume Labs (<100 Assays/Month)	HercepTest 3+	10/52	12/52	10/52 (19%)
	Other IHC pos.	11/23	9/23	8/23 (35%)
	Total	21/75	21/75	18/75 (24%)
Initial Test Done at Large-Volume Labs (100+ Assays/Month)	HercepTest 3+	1/28	1/28	1/28 (4%)
	Other IHC pos.	0/1	0/1	0/1 (0%)
	Total	1/29	1/29	1/29 (3%)

From Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing: National Surgical Adjuvant Breast and Bowel Project experience. *J Natl Cancer Inst.* 2002;94:852-854. By permission of Oxford University Press.

appears to be ineffective when the FISH test demonstrates nonamplification.

Thus, trastuzumab should be considered for use only in breast cancer patients with a tumor that is IHC 3+ or in the “unfavorable” IHC category or have a HER2:CEP 17 ratio of ≥ 2 . Those with an IHC HER2 expression of 2+ should be treated with trastuzumab only if a confirmatory FISH test was done and the result was positive.

Cardiac Toxicity

Trastuzumab is generally well tolerated. Hypersensitivity reactions are usually restricted to the period during or immediately following the first injection. After recovery from such a reaction, some patients have been re-treated together with prophylactic premedication. Some of these patients tolerated re-treatment, but others had reactions again.¹⁰ Hematologic toxicity is infrequent, but anemia and leukopenia may be observed in patients who receive both trastuzumab and chemotherapy. Diarrhea has also been reported.¹⁰ Cardiac toxicity, however, is the side effect of greatest clinical concern with trastuzumab treatment.

Cardiac dysfunction was an unexpected finding in the phase II trials of trastuzumab, so the data on incidence and severity of this complication are based on retrospective evaluation. Table 3 summarizes the reported incidence of cardiac toxicity in early trials of patients with metastatic disease.⁴ There was a 4% risk of cardiac dysfunction in patients treated with trastuzumab alone, which resolved in 50% of patients after treatment. The highest risk of cardiac dysfunction (27%) occurred when trastuzumab was given together with anthracycline plus cyclophosphamide, and it was

noted in 13% of patients treated with trastuzumab plus paclitaxel. It is of note that cardiac dysfunction also occurred (8%) after treatment with anthracycline plus cyclophosphamide alone. The continued use of trastuzumab did not cause further deterioration of cardiac function in the majority of patients so managed; in nearly all cases, cardiac function improved after treatment with standard therapy.^{11,12}

The pathogenesis of trastuzumab-associated cardiotoxicity is not clear, although it is known that HER2 plays a role in embryonic cardiogenesis,¹³ and one clinical study reported myocardial uptake of radiolabeled trastuzumab in 7 of 20 patients treated with trastuzumab.¹⁴ Six of these 7 patients developed cardiotoxicity, but none of the 13 with no cardiac uptake had the complication. The possibility that trastuzumab amplifies or has an additional cardiotoxic effect when administered after anthracycline therapy has also been postulated.¹⁵

Trastuzumab-associated cardiac toxicity differs from anthracycline-associated cardiac toxicity in at least three ways. First, whereas the risk of anthracycline-induced cardiotoxicity increases with increasing cumulative dose,¹⁶ there is no evidence that the same association holds true for trastuzumab treatment. Some patients have received trastuzumab for many years without developing cardiac events. Second, severe cardiac toxicity is associated less often with trastuzumab than with anthracyclines, and cardiac effects are at least partially reversible.^{11,12} Most patients have improvement in functional class and ejection fractions after treatment of heart failure or stopping trastuzumab. Lastly, cardiac biopsies performed on 6 patients at the M. D. Anderson Cancer Center have revealed no morphologic changes similar to anthracycline-induced cardiomyopathy.¹²

Table 3. — Incidence of Cardiac Dysfunction in a Randomized Comparative Clinical Study of Trastuzumab Plus Chemotherapy vs Chemotherapy Alone and in Pooled Studies of Trastuzumab Monotherapy

	Incidence (%)				
	Trastuzumab			Anthracycline plus cyclophosphamide monotherapy (n = 91)	Paclitaxel monotherapy (n = 95)
	Monotherapy (n = 338)	Plus anthracycline plus cyclophosphamide (n = 143)	Plus paclitaxel (n = 135)		
Cardiac dysfunction	4.0	27.0	13.0	8.0	1.0
Grade 3 or 4 (initial)	3.0	16.0	2.0	3.0	1.0
Grade 3 or 4 (posttreatment)	1.5	6.0	0	0.7	0
Death from cardiac dysfunction	0.9	0.7	0	0.7	0

Data adapted from Slamon DI, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344:783-792, and from Baselga J. Safety profile of Herceptin as a single agent and in combination with chemotherapy (abstract 1299). *Eur J Cancer.* 1999;35:5324. Copyright 1999, reprinted with permission from Elsevier Science.

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The two factors that are clearly associated with an increased risk of trastuzumab-associated cardiotoxicity are age over 60 years and concurrent treatment using trastuzumab plus an anthracycline.¹⁷ Other factors suspected of predisposing toward trastuzumab cardiac toxicity include a prior anthracycline dose ≥ 400 mg/m², prior chest wall irradiation, and preexisting cardiac dysfunction. Tachycardia may be an early indicator of trastuzumab-associated cardiotoxicity, and measurement of this parameter is included in guidelines used at the Memorial Sloan-Kettering Cancer Institute to direct a formal assessment of cardiac function (Table 4).¹¹ The measurement of left ventricular ejection fraction (LVEF) by multigated acquisition (MUGA) scanning is noninvasive and is the most commonly used tool for clinical monitoring of the heart during trastuzumab therapy. However, the significance of a fall in LVEF if the patient is asymptomatic patients, however, is unknown. Echocardiography is an alternate noninvasive tool that can identify both systolic and diastolic dysfunction as well as valvular and pericardial disease. Clinical guidelines for monitoring cardiac function before and during treatment with trastuzumab as well as guidance on managing trastuzumab-associated heart failure are now available.¹¹

More prospective data on changes in LVEF during trastuzumab treatment are emerging from the adjuvant and neoadjuvant studies that are evaluating the benefits of incorporation of trastuzumab into adjuvant chemotherapy protocols (Figure). To date, several thousand women have been entered onto these adjuvant trials. Participants in the adjuvant trials have both baseline and subsequent monitoring for cardiac events included as an integral part of the studies.

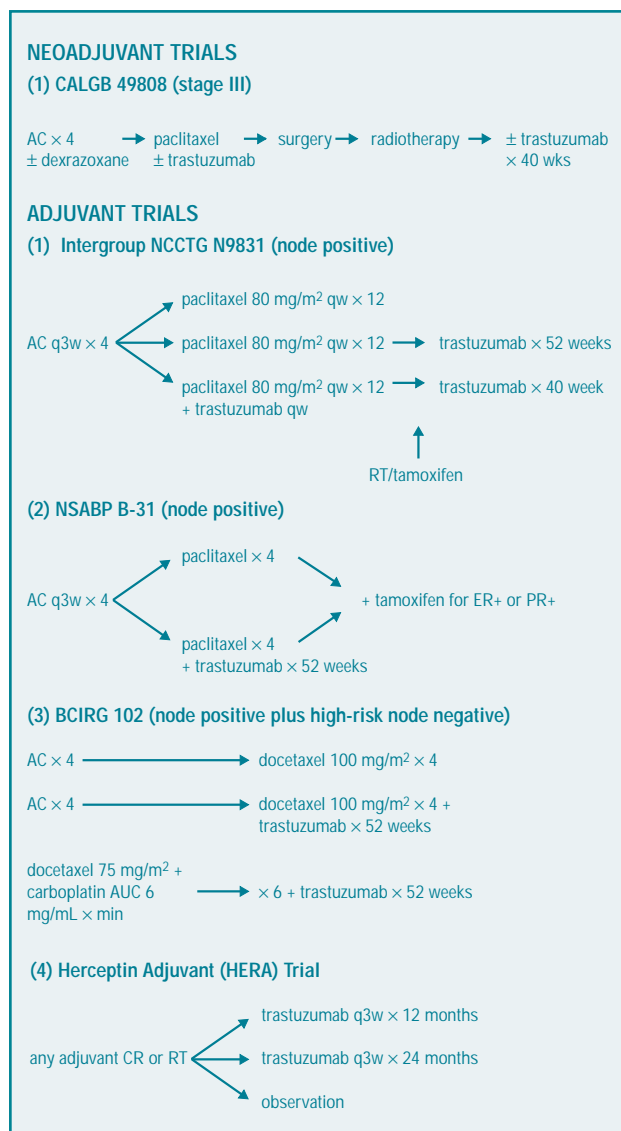
Preliminary reports from these adjuvant studies indicate that some patients have a reduced LVEF after standard-dose doxorubicin plus cyclophosphamide (AC) treatment. For example, 5% of 1,044 women who completed AC treatment in the intergroup NCIG N9831 study fit the study criteria for prohibition of

starting trastuzumab (E. Perez, MD, personal communication, September 2002). Arm 3 of this study was temporarily suspended in 2002 because of concern about cardiac events, but this arm has subsequently been reopened for case accrual, suggesting that the incidence and severity of trastuzumab-related cardiac events in these adjuvant studies is small. Indeed, this study is to be expanded to include high-risk node-negative patients.

Metastatic Breast Cancer

Schedule

The most commonly used schedule for trastuzumab is a "loading" intravenous dose of 4 mg/kg given as a 90-minute infusion and followed by a weekly "mainte-



Schema of selected clinical studies of trastuzumab in neoadjuvant and adjuvant therapy for breast cancer.

nance” dose of 2 mg/kg that can be given over 30 minutes if the initial dose was well tolerated.¹⁰ Studies of higher loading and maintenance doses have not demonstrated increased activity,³ but the mean half-life of trastuzumab increases and clearance decreases with increasing doses, and the half-life of trastuzumab in the serum is now estimated to be approximately 30 days.¹⁸ Gelmon et al¹⁹ have reported that a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg given every 3 weeks provides serum trastuzumab concentrations equivalent to those achieved by the “standard” weekly dosing regimen. This alternate dosing regimen will likely be shown to be as effective and is more convenient than the weekly dosing regimen. It is now being incorporated into some clinical trials, including adjuvant trials, and it seems a reasonable choice to be included in standard clinical practice.

Trastuzumab Monotherapy

Two large trials have evaluated the antitumor effectiveness of trastuzumab alone in patients with HER2 overexpressing metastatic tumors. The first was a “salvage” trial and included 222 patients with prior chemotherapy.² Nevertheless, trastuzumab monotherapy gave a response rate (complete [CR] and partial [PR]) of 15%, and responses lasted 9.1 months. A trial by Vogel et al³ studied patients at an earlier stage and reported a response rate (CR and PR) of 26% and clinical benefit (CR, PR, and stable >6 months) occurring in 38% of patients treated, with a median duration of response of 18.8 months. This salutary response rate suggests that trastuzumab alone might be a reasonable choice for those patients with a relatively limited extent of metastatic disease (eg, having similar tumor spread characteristics as patients who might be considered for hormonal therapy). Such early treatment with trastuzumab monotherapy would not seem to abrogate the effectiveness of later treatment with trastuzumab plus chemotherapy. In a phase II study by Burris et al,²⁰ patients were treated initially with trastuzumab alone and obtained a 21% incidence of response. Subsequent treatment with paclitaxel plus

carboplatin induced responses in 11 of 20 responses. This rate is consistent with reports of combined trastuzumab-chemotherapy treatment given as “first-line” therapy.⁴

Combination With Chemotherapy

The seminal report by Slamon et al⁴ demonstrated the now well-known information that, in patients with HER2-overexpressing metastatic breast cancer, the addition of trastuzumab to chemotherapy increases response rates, prolongs the duration of remissions, and lengthens survival in comparison to treatment with chemotherapy alone (Table 1). Deserving reemphasis is the finding that the chemotherapy-trastuzumab combination was associated with a 5-month longer median survival even though 67% of patients randomized to receive chemotherapy alone initially subsequently received trastuzumab. This suggests that “early” use of trastuzumab, ie, given with the first line of chemotherapy in patients with metastatic disease, is optimal.

Trastuzumab adds to the clinical benefit of several other chemotherapeutic drugs besides the doxorubicin/cyclophosphamide doublet and paclitaxel therapies reported by Slamon and associates. Taxanes have been further studied (Table 5),²¹⁻²³ and combinations of trastuzumab with vinorelbine produce response rates that are often over 60% (Table 6).²⁴⁻²⁶ Response rates are always highest in those patients who have IHC 3+ or FISH+ test results.

Other agents that have been successfully combined with trastuzumab include gemcitabine²⁷ and capecitabine.²⁸ Despite the known association of cardiac toxicity with anthracycline-containing regimens, studies are in progress using liposome-encapsulated doxorubicin²⁹ and epirubicin³⁰ (Table 7).

Of great current interest is the use of trastuzumab with platinum plus taxane combinations (Table 8). Pegram et al³¹ demonstrated a 24% incidence of response and a 48% incidence of clinical benefit in

Table 5. — Selected Trials of Trastuzumab Plus Taxanes in Patients With HER2-Overexpressing Metastatic Breast Cancer

Author (reference)	“Line” of Therapy	Dose/Schedule	Objective Response Rate
Slamon et al (4)	After anthracycline	paclitaxel 175 mg/m ² q 3 weeks	50%
Seidman et al (21)	1st, 2nd, or 3rd	paclitaxel 90 mg/m ² q week	57%
Esteva et al (22)	After anthracycline	docetaxel 35 mg/m ² d 1, 8, 15 q 28 days	63%
Burris et al (23)	1st or 2nd	docetaxel 75 mg/m ² q 3 weeks	54%

chemoresistant HER2-positive breast cancer using trastuzumab plus cisplatin. Since then, tolerance and toxicity concerns concerning cisplatin have stimulated evaluation of carboplatin-taxane doublets given either weekly²⁰ or every 3 weeks. As examples, investigators at UCLA³² have evaluated a combination of docetaxel plus carboplatin given each 3 weeks together with weekly trastuzumab. In their patients who were FISH+, there was a 64% response rate (CR plus PR) to that combination in comparison to a 41% rate for those who were FISH-. A US Oncology group entered 196 patients with metastatic breast cancer who were HER2, 2+, 3+ or FISH+ into a study (N. Robert, MD) personal communication, September 2002) comparing paclitaxel

given every 3 weeks plus weekly trastuzumab vs paclitaxel plus carboplatin given every 3 weeks plus weekly trastuzumab. The combination arm was more toxic but provided more responses that were of significantly longer duration than the paclitaxel/trastuzumab-alone arm. These data support trials of this approach for adjuvant therapy in high-risk breast cancer patients.

Combination With Hormones

Many questions arise regarding optimal management of patients with tumors that are characterized as being both estrogen receptor (ER)-positive and HER2-positive. This combination of tumor characteristics has

Table 6. — Selected Trials of Trastuzumab Plus Vinorelbine in Patients With HER2-Overexpressing Metastatic Breast Cancer

Author (reference)	"Line" of Therapy	Vinorelbine Dose/Schedule	Objective Response Rate
Burstein et al (24)	1st, 2nd, and 3rd (IHC 2+, 3+)	25 mg/m ² /IV/week	75%
Jahanzeb et al (25)	1st line (IHC 2+, 3+)	30 mg/m ² /IV/week	78%
Burstein et al (26)	1st line (IHC 3+ or FISH+)	25 mg/m ² /IV/week	68%

IHC = immunohistochemistry
FISH = fluorescence in situ hybridization

Table 7. — Selected Trials of Trastuzumab Plus Other Chemotherapy in Patients With HER2-Overexpressing Metastatic Breast Cancer

Author (reference)	"Line" of Therapy	Dose/Schedule	Objective Response Rate
O'Shaughnessy et al (27)	extensively pretreated	gemcitabine 1200 mg/m ² d1 and d8 q 21 days	37%
Bangemann et al (28)	salvage	capecitabine 2000 mg/m ² d1-14 q 21 day	53%
Theodoulou et al (29)	2nd or later	TLC D99 (liposomal doxorubicin)	58%
Untch et al (30)	not stated	epirubicin 60 mg/m ² plus cyclophosphamide	not stated

Table 8. — Selected Trials of Trastuzumab Plus a Platin or With a Platin Plus a Taxane in Patients With HER2-Overexpressing Metastatic Breast Cancer

Author (reference)	"Line" of Therapy	Dose/Schedule	Objective Response Rate
Pegram et al (31)	extensively pretreated	cisplatin 75 mg/m ² q 28 days	24.3%
Slamon et al (32)	1st line 67% prior adjuvant chemotherapy	docetaxel 75 mg/m ² q 21 days plus carboplatin AUC 6 q 21 days	54%
Pienkowski et al (33)	1st line 56% prior adjuvant chemotherapy	docetaxel 75 mg/m ² q 21 days plus cisplatin 75 mg/m ² q 21 days	76%
Burris et al (20)	prior trastuzumab	paclitaxel 70 mg/m ² /week plus carboplatin AUC 2/week	55%
Nabholtz (34)	1st line, FISH+	docetaxel 75 mg/m ² q 3 weeks plus carboplatin AUC 6 q 3 weeks	64%
N. Robert, MD (personal communication)	1st line (IHC 3+) vs 1st line (IHC 3+)	paclitaxel 175 mg/m ² q 3 weeks paclitaxel 175 mg/m ² plus carboplatin 175 mg/m ² q 3 weeks	38% 52%

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implications both for prognosis and for predicting response to treatment. The Naples GUN adjuvant trial³⁵ suggested that use of tamoxifen in such patients might be detrimental to survival, but this study contains many flaws. Many clinicians believe that the response of breast cancer patients to hormone therapy with tamoxifen is diluted in HER2-positive patients. Lipton et al³⁶ have described a shorter time to progression in patients with metastatic breast cancer treated with hormones who had elevated levels of circulating HER2 in comparison with those who did not. Ellis et al³⁷ evaluated responses to neoadjuvant tamoxifen or letrozole in postmenopausal patients with locally advanced HER1/2-positive tumors who were also ER-positive, and compared outcomes to patients who had ER-positive, HER1/2-negative tumors (Table 9).

The numbers are small but suggest that an aromatase inhibitor might be capable of at least partially ameliorating primary tamoxifen resistance. Two important studies are now in progress that will assess whether trastuzumab can enhance responses to aromatase inhibitors in postmenopausal women with HER2-positive and ER-positive metastatic tumors. One is a phase II study that evaluates the combination of letrozole plus trastuzumab. Another is a phase III study that compares anastrozole alone to anastrozole plus trastuzumab. In the adjuvant therapy situation, it seems reasonable to recommend the appropriate adjuvant hormonal therapy based on the ER-positivity of the tumor for patients with clinically localized ER-positive and HER2-positive tumors and not modify the approach based on the HER2-positivity.

Duration of Therapy With Trastuzumab

When trastuzumab is prescribed for patients with HER2-positive metastatic breast cancer, either alone or in combination with cytotoxic chemotherapy, the drug is usually continued for as long as clinical benefit ensues, even if the cytotoxic therapy component of the intervention is discontinued because of toxicity or intolerance. Thus, in the absence of severe toxicity

(eg, cardiac toxicity), the drug may be administered for long periods, sometimes several years. Questions arise, however, when the breast cancer progresses. Should trastuzumab be stopped or continued? Should an alternate hormone or cytotoxic agent be used — alone or with trastuzumab? Since trastuzumab is a growth inhibitor, should it be continued indefinitely akin to the policy of ensuring life-long androgen blockade in patients with metastatic prostate cancer even in the face of progressive metastatic disease?³⁸

A decision on continuing trastuzumab after progression from management with trastuzumab alone or if combined with a hormone is relatively easy. There is an excellent chance of clinical response occurring if a drug combination of proven effectiveness (eg, trastuzumab plus a taxane or vinorelbine or a taxane/carboplatin doublet) were prescribed, and such an approach will generally be indicated. What approach should be used, however, if a patient has responded to a combined trastuzumab-chemotherapy approach and has then progressed?

One relevant clinical study in progress randomizes treatments to patients who have progressed after trastuzumab plus a taxane between vinorelbine alone and vinorelbine plus trastuzumab. Until data from such important trials are at hand, we are forced to rely on the retrospective data collection on first and second-line use of trastuzumab reported by Mackey et al³⁹ recognizing the inherent limitations of nonprospective data. First-line trastuzumab monotherapy was associated with a response rate of 41%, and the combination of trastuzumab plus a taxane 38%. Second-line trastuzumab therapy provided similar objective response rates, ie, 38% with a combination with a taxane and 27% with a combination with vinorelbine (Table 10). The similarity of the reported outcomes between first- and second-line usage suggests that it is reasonable to consider a different trastuzumab/chemotherapy combination as second-line treatment after failure or progression from an initial trastuzumab-chemotherapy combination.

Table 10. — Retrospective Evaluation of Treatment Outcomes From First- and Second-Line Trastuzumab Treatment

	Response Rate	Time to Progression
First Line:		
Monotherapy (n = 27)	41%	23 weeks
Combination with taxane (n = 50)	38%	24 weeks
Second Line:		
Monotherapy (n = 11)	36%	24 weeks
Combination with taxane (n = 21)	38%	26 weeks
Combination with vinorelbine (n = 27)	27%	30 weeks
Data from Mackey et al. ³⁹		

There are no good data to help direct use of third or later lines of trastuzumab combined with chemotherapy, so clinical judgment needs to be used. If the disease progression is relatively slow and the patient is in good clinical condition, then trial of a third trastuzumab/chemotherapy combination could be considered. However, if there was no response to prior trastuzumab/chemotherapy combinations and disease progression is rapid, then it is probably reasonable to discontinue trastuzumab. In situations where the central nervous system (CNS) is the sole site of progression and systemic metastasis is well controlled, there is logic to continuing the trastuzumab with or without other chemotherapy treatment while managing the CNS metastasis appropriately.

Trastuzumab in Adjuvant Therapy

The effectiveness of trastuzumab plus chemotherapy in patients with HER2-positive metastatic breast tumors,⁴ particularly since survival was prolonged, has generated great interest in the adjuvant arena. The largest currently active trials are summarized in the Figure.

Accrual to these studies has been rapid, with over 1,000 patients having been entered onto many of the studies. An important concern with these studies is, of course, cardiac toxicity, and only patients screened to exclude those with preexisting cardiac problems are entered. Concern was heightened when accrual to arm 3 of the Breast Intergroup Trial N9831 was interrupted in early 2002 because of an apparent excess of cardiac events in that arm of the study. The study protocol safety and monitoring board has since lifted the proscription on case entry, however, suggesting that cardiac events were either not severe or not occurring at high rates or both. In addition, accrual to this protocol will soon include high-risk node-negative patients. Initial reporting on cardiac toxicity from the studies (E. Perez, MD, personal communication, September 2002) indicates that some patients have experienced a minor decline in LVEF after standard-dose doxorubicin plus cyclophosphamide therapy. Overall, the rates of cardiac events from trastuzumab alone or trastuzumab plus chemotherapy in these adjuvant or neoadjuvant studies seem to be low.

Most adjuvant studies in the United States are studying a 1-year duration of trastuzumab treatment, although the HERA study includes an arm with 2 years of treatment. One can speculate if a longer duration of adjuvant therapy should be studied using the example of tamoxifen where a 5-year treatment duration is appreciably superior to 1 year of treatment.⁴⁰

Central Nervous System Metastases

It is perhaps not surprising that breast cancer patients with HER2-overexpressing tumors are at high risk for developing CNS metastases — either parenchymal brain or meningeal metastases. In part, this may be due to the fact that treatment with trastuzumab is allowing patients with HER2 overexpressing metastatic disease to live longer than they previously did, thus allowing more chance for tumor growth in the “sanctuary” of the CNS to occur and become evident. The incidence of this complication seems sufficiently high that it may be reasonable to include imaging of the brain in the initial tumor staging assessment of a patient with metastatic HER2-overexpressing breast cancer even in the absence of CNS symptoms and signs.

Since CNS metastases often occur when the non-CNS component of metastases is under good control by a treatment program including trastuzumab, it seems reasonable to continue the systemic approach for these patients as the CNS metastases are treated essentially independently. Studies of prophylactic treatment to delay or prevent brain metastasis in HER2 overexpressors have not been reported.

Conclusions

Since there is now a more uniform realization that breast cancer patients will derive benefit from trastuzumab only if the tumor is found to overexpress HER2 either by a 3+ or “unfavorable” IHC result or by a positive FISH test performed by a high-volume laboratory, there should be better discrimination as to which patients should receive the drug. Benefits accrue when the drug is prescribed alone or with a variety of cytotoxic antitumor agents and possibly hormones. Trastuzumab-associated cardiac disease remains a concern but appears to be a different entity than anthracycline-induced cardiac disease and is often reversible. Issues regarding the length of time that trastuzumab is prescribed after progression of disease are still open.

Adjuvant trials of trastuzumab plus chemotherapy are well underway, with rather reassuring early reports that suggest a low incidence of significant cardiac events. Results from studies that combine trastuzumab with other novel biologic agents are awaited with interest.

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