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Review paper

Duration of therapy in metastatic breast cancer: management using Herceptin®

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Despite progressive developments in therapeutic interventions, including surgery, radiotherapy and chemotherapy, there has been no major improvement in the survival of women with metastatic breast cancer (MBC). Based on knowledge of tumor growth patterns, approaches addressing this issue have included increasing chemotherapy dose or dose density and extending the duration of therapy. However, only the latter approach has resulted in improved clinical benefit, although not survival; and its use is restricted by the cumulative toxicity of chemotherapeutic agents. Therefore, the best hope for improved survival lies with new classes of anticancer drug and particularly biological agents. This review focuses on the first oncogene-targeted therapy for human epidermal growth factor receptor-2 (HER2)$^+$ MBC patients. The humanized anti-HER2 monoclonal antibody Herceptin® has proven clinical benefits in HER2$^+$ MBC patients, most importantly improved survival, and is rapidly becoming a standard of care for these patients. In contrast to the fixed number of cycles used for chemotherapeutic agents, Herceptin is administered until disease progression, with some data suggesting that continuation beyond disease progression should be investigated. The preclinical and clinical findings on which the current recommended duration of Herceptin therapy are based are reviewed and alternative strategies are discussed.

Key words: Breast cancer, Herceptin®, survival, treatment duration, tumor growth.

Introduction

Advances in the field of medical oncology have resulted in anticancer drugs joining surgery and radiotherapy as effective interventions in the routine management of most stages of breast cancer.[1] However, despite improvements in time to disease progression, time to treatment failure and quality of life (QoL), the lack of significant improvement in survival in patients with metastatic breast cancer (MBC) remains a major concern.[2–6] This failure to improve survival could be due to the failure of chemotherapy to affect the natural history of MBC.

Research into tumor cell growth provided the intellectual framework and rationale for the current widespread use of combination chemotherapy. However, the optimal duration of chemotherapy has not been established,[2] at least in part because drug-related toxicity prevents extended-duration therapy despite data showing that this approach increases clinical benefit.[7,8] Therefore, research is now focused on developing novel therapies that are effective but less toxic than chemotherapy. These new agents may have an important role in the management of patients with MBC due to their favorable safety profiles and lack of cumulative toxicity. Furthermore, the use of agents with novel mechanisms of action may enhance the effects of current cytotoxic chemotherapy regimens. This has a precedent in early breast cancer with evidence showing that chemotherapy and hormonal therapy are complementary, and that the combination produces additional benefits over those of chemotherapy alone.[9,10]

Targeting the human epidermal growth factor receptor-2 (HER2) is a unique example of a biological approach to treating advanced breast cancer. The identification of HER2,[11] the recognition that it has prognostic and potential predictive significance,[12–14] and its role as an oncogene in the development of breast cancer[15] made it an attractive target for anticancer therapy. This led to investigation of a range of biological approaches to targeting HER2.[16–22] The humanized anti-HER2 monoclonal antibody (mAb) Herceptin® (trastuzumab) targets the cell surface HER2 receptor, which has growth-modulating activity. Herceptin is the first anti-HER2 therapy developed to date with proven clinical efficacy and tolerability in patients with HER2$^+$ MBC.[23–30]

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The rapid development and introduction of Herceptin into the clinic have resulted in significant issues in regard to its optimal use, particularly in relation to when to initiate therapy, whether to use monotherapy or combination therapy and which agent(s) to combine Herceptin with, and how long to continue therapy. The first two of these issues have been and continue to be addressed in clinical trials, with current data indicating that Herceptin is effective and generally well tolerated as monotherapy and in combination with various cytotoxic agents, and that efficacy increases when it is used upfront in the metastatic setting.[24,27,29–31] In terms of treatment duration, the current recommendation is that Herceptin should be used until disease progression without dose modification. This recommendation is based on preclinical and clinical data, as well as consideration of cancer cell growth kinetics, and their role in determining the most appropriate dose and duration of cancer therapy. Other strategies have not been tested. This review discusses the implications of cancer cell growth kinetics for the use of biological therapies whose major effect is not cytotoxicity, using Herceptin as a specific example. The rationale for using Herceptin until disease progression is discussed in detail.

Kinetics of cancer cell growth and optimizing anticancer therapy

The Skipper–Schabel hypothesis was one of the earliest attempts to explain the activity of anticancer drugs and states that a given dose of a specific drug kills a fixed fraction rather than an absolute number of cancer cells.[32,33] While this is true of tumors that grow exponentially, most tumors display non-exponential growth kinetics. Research has demonstrated that cell kill is proportional to tumor growth rate, which decreases as tumor size increases.[7] This results in a sigmoid growth pattern characterized by growth that is greatest when tumors are smallest.[7] The significance of this is that smaller tumors tend to regrow faster between cycles of chemotherapy than larger tumors. Thus, antitumor effects during treatment need to be optimized while tumor regrowth between treatment cycles is prevented.

A variety of approaches to optimizing the anticancer effects of chemotherapy have been used. Despite conflicting evidence on the importance of chemotherapy dose,[34–36] one of the most common approaches is dose intensification by dose escalation.[34] However, the benefits in terms of cell kill produced by higher doses have not realized clinical benefit, possibly due to the rapid regrowth of tumor cells. Another approach is to increase dose density by reducing the time between treatment cycles. Both alternating and sequential schedules are capable of delivering drugs at recommended doses, with sequential dosing potentially providing the optimal dose density for each individual agent. This approach has been shown to be more effective than alternating schedules.[37–40] However, toxicity remains a problem and the clinical efficacy of both of these approaches appears to be restricted by a limit to the magnitude of cytoreduction.[41] Peters *et al.* have shown that the survival duration of MBC patients treated with high-dose consolidation chemotherapy at complete response (CR) is shorter than that of patients who received the same therapy at relapse of CR.[35] These data suggest a lack of clinical benefit from high-dose/dose-dense approaches in MBC.

Biological factors affect both prognosis and response to therapy in MBC. For example, HER2 gene amplification/protein overexpression is associated with more aggressive disease, shortened disease-free and overall survival,[13,14] and altered responses to conventional anticancer agents.[42,43] These findings have stimulated research into biological agents that are directed against the quantitatively abnormal growth factor receptors that determine this adverse phenotypic behavior. One of the aims of these research efforts is to enhance the efficacy of existing anticancer treatment by inhibiting tumor cell regrowth. Furthermore, targeting tumor cells should potentially reduce the incidence of side effects. Thus, biological agents hold the promise of controlling tumor growth over long time periods, suggesting a need to change the anticancer treatment paradigm.

Extended-duration therapy is not a widely accepted *or practical* concept in cancer management, with the exception of the use of tamoxifen in chemoprevention and adjuvant therapy to prevent relapse.[44] However, data show that longer-duration chemotherapy produces better median time to disease progression and increased QoL compared to shorter durations of the same regimens until progression of disease,[2–6,45] but does not have a significant impact on patient survival.[3,6] For this reason, current practice is generally a compromise, with chemotherapy being continued until maximal response to achieve a balance between benefit and drug-related toxicity.[2] However, biological agents such as Herceptin may provide additional benefit by virtue of not having cumulative toxicity, allowing use beyond maximal response. The rationale for this approach to the use of Herceptin is discussed below.

Targeting HER2$^+$ breast cancer with Herceptin

Herceptin is the result of a rational development process in which HER2 amplification/overexpression was identified as a tumor-associated abnormality with a role in cancer pathogenesis and prognosis, making it a potential therapeutic target.[12–15] Murine anti-HER2 mAb were the first method of targeting the receptor to be investigated, and the antibody designated 4D5 was shown to have greatest specificity for HER2$^+$ cells. To overcome the problem of neutralization of murine antibodies by the human immune system, 4D5 was humanized. This involved combining the hypervariable antigen-binding portions of the murine antibody with a human immunoglobulin variable framework using recombinant DNA technology to produce a humanized antibody with specificity similar to that of the murine antibody.[18]

Preclinical studies of Herceptin

Early studies demonstrated that Herceptin exerts a cytostatic effect on breast cancer cells overexpressing HER2, downregulates the number of HER2 receptors on the cell surface and supports antibody-dependent cellular cytotoxicity (ADCC) against human tumor cell lines, but has no impact on healthy HER2$^-$ cells.[18,46,47] Furthermore, synergistic and additive cytotoxic effects were observed when Herceptin was combined with chemotherapeutic agents including cisplatin, paclitaxel and doxorubicin both *in vitro* and in mouse xenograft models of breast cancer.[48–50] Importantly, withdrawal of Herceptin treatment in preclinical models resulted in rapid tumor regrowth (Figure 1).[50] This suggests that the presence of Herceptin is required for continued tumor suppression.

Clinical trial experience with Herceptin

A number of phase II and III trials have been conducted with Herceptin either as monotherapy or in combination with chemotherapy in HER2$^+$ MBC patients.[24–30] Most of these studies have used the standard regimen of a 4 mg/kg i.v. initial dose followed by a 2 mg/kg weekly i.v. infusion of Herceptin until disease progression.

Single-agent Herceptin. Two major phase II trials of Herceptin monotherapy have been conducted, both of which demonstrated that Herceptin has significant clinical benefit.[25,29,30] In both trials, Herceptin was administered until disease progression. When used as second- or third-line monotherapy in heavily pretreated HER2$^+$ women with stage IV breast cancer, Herceptin produced an overall response rate of 15%, and a median duration of response and survival of 9.1 and 13 months, respectively.[25] Furthermore, in patients who were strongly HER2$^+$ the response rate was 18% and response duration increased to 16.4 months. These results were confirmed by an independent Response Evaluation Committee. The observed benefit was greater when Herceptin was used as first-line monotherapy: the overall response rate was 26% and a further 12% of patients had stable disease for longer than 6 months.[29] The greater benefit of Herceptin in strongly HER2$^+$ patients observed in the pivotal monotherapy trial was also observed in this trial: the response rate was 35% and survival was 24.4 months.[30]

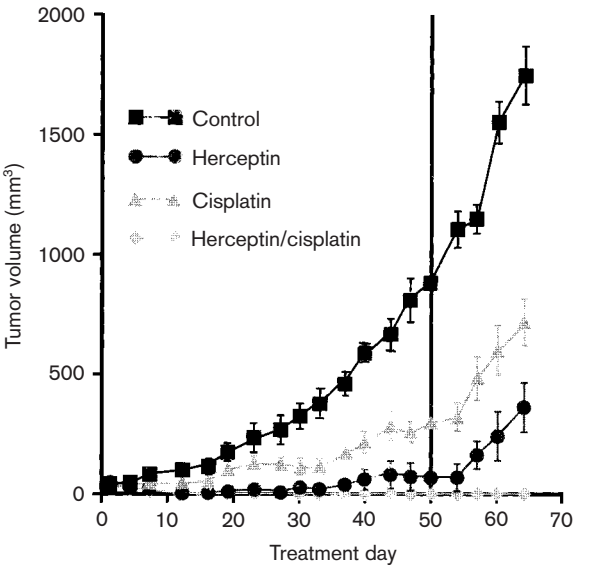

Figure 1. Effect of cyclic therapy with cisplatin plus Herceptin on the growth of MCF-7/HER2 breast tumor xenografts in nude mice. Reproduced, with permission, from Pietras *et al.*[50]

Importantly, these studies demonstrated that the side effects associated with Herceptin are generally mild to moderate in severity and infusion related.[25] Typically, patients may experience fever and chills with the first dose of Herceptin. Other infusion-related symptoms include nausea, headache, pain, asthenia and dyspnea. These symptoms are manageable and usually resolve during the infusion. The most significant event associated with treatment in these trials was cardiotoxicity, which affected 4.7% of patients who received second/third-line Herceptin monotherapy and 2.6% of patients who received first-line monotherapy.[25,29,30] The majority of these patients

had underlying cardiac disease and prior anthracycline exposure or risk factors for anthracycline-induced cardiotoxicity. Most patients improved with standard cardiac therapy whether or not Herceptin was withdrawn.

Herceptin monotherapy is also associated with QoL benefits. Lieberman *et al.* demonstrated that health-related QoL was maintained while patients were receiving Herceptin in the trial of second/third-line monotherapy, i.e. until disease progression.[51] First-line Herceptin monotherapy produced similar benefits and it was concluded that in terms of clinically meaningful health-related QoL most patients achieve benefit from Herceptin therapy or at worse do not experience deleterious effects.[52]

Herceptin in combination with chemotherapy. The studies of Herceptin monotherapy demonstrated that it has significant antitumor activity, is generally well tolerated and has a positive impact on QoL for the duration of its use. These features, together with preclinical data on synergy,[48–50] suggest a role for combination with chemotherapy. Clinical trials reported to date have demonstrated that the addition of Herceptin, administered until disease progression, to paclitaxel, anthracycline/cyclophosphamide (AC), docetaxel and vinorelbine produces clinical benefit greater than that of chemotherapy alone (Table 1).[24,27,28,31] The largest of these trials, a multicenter, randomized, open-label, phase III trial involving 469 $HER2^+$ patients, demonstrated that adding Herceptin to first-line chemotherapy (AC or paclitaxel) significantly prolonged median time to disease progression, increased the overall response rate and prolonged median response duration.[28] Most importantly, the combination of Herceptin plus chemotherapy increased overall survival from 20.3 to 25.1 months after a median of 30 months follow-up. Furthermore, when strongly $HER2^+$ patients were evaluated separately after 35 months of follow-up, overall survival was shown to increase by 45% from 20 months in patients treated with chemotherapy to 29 months in those treated with Herceptin plus chemotherapy (Figure 2).[53] These survival benefits were observed despite 65% of all chemotherapy-alone patients subsequently being treated with Herceptin at disease progression. This cross-over design was included in the original study protocol.[28] These observations strongly suggest that the survival benefit of Herceptin is achieved when Herceptin is used early rather than late.

In these combination therapy studies, Herceptin treatment did not significantly increase the incidence or severity of side effects normally associated with the various chemotherapeutic agents studied.[24,27,28,31,54] The infusion-related symptom complex of mild-to-moderate fever and chills was the most common Herceptin-related event. This favorable safety profile is reflected in trends toward improvement in QoL noted with Herceptin combination therapy.[54]

Table 1. Clinical benefit of Herceptin

Study	Herceptin regimen	Concomitant therapy	Response rate (%)	Median time to progression (months)	Overall survival (months)
Cobleigh *et al.*[25]	4 mg/kg i.v. followed by 2 mg/kg weekly until progression	–	15	3.1	13
Vogel *et al.*[29] [a]	8 or 4 mg/kg i.v. followed by 4 or 2 mg/kg. i.v. weekly until progression	–	27 versus 25	3.8 versus 3.5	25.8 versus 22.9
Slamon *et al.*[28] [b]	4 mg/kg i.v. followed by 2 mg/kg weekly until progression	3-weekly AC or paclitaxel	50 versus 32 (p=0.001)	7.4 versus 4.6 (p=0.001)	25.1 versus 20.3 (p=0.046)
Burstein *et al.*[28] [b]	4 mg/kg i.v. followed by 2 mg/kg weekly until progression	Vinorelbine	75	–	–
Seidman *et al.*[27] [c]	4 mg/kg i.v. followed by 2 mg/kg weekly until progression	Weekly paclitaxel	62	–	–
Kuzur *et al.*[31]	4 mg/kg i.v. followed by 2 mg/kg weekly until progression	3-weekly docetaxel	54	>6	–

[a]Data are shown for patients who received 4 mg/kg followed by 2 mg/kg i.v. and those who received 8 mg/kg followed by 4 mg/kg i.v. until progression, respectively. Outcomes in these two dose groups were similar.
[b]Data for patients who received Herceptin plus chemotherapy and chemotherapy alone, respectively, are shown. Note that 65% of patients who progressed on chemotherapy alone crossed over to received Herceptin.
[c]Response rate in patients who were $HER2^+$ using the Hercep Test®.

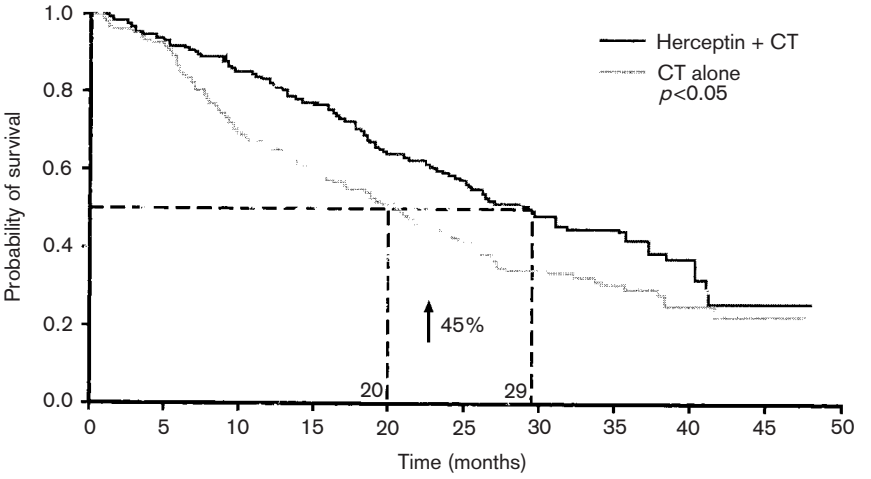

Figure 2. Overall survival following treatment with Herceptin plus chemotherapy in women with metastatic breast cancer overexpressing HER2 at the 3+ level.

As was observed in the monotherapy trials, the most clinically significant adverse effect associated with Herceptin in these studies was cardiac dysfunction.[24,27,28,31,55] These studies produced additional information indicating that cardiac events occur predominantly when Herceptin is used concurrently with an anthracycline and occur at a significantly lower rate (8.6%) when the drugs are used sequentially, i.e. using Herceptin in women who have received prior anthracycline therapy.[28,55] Further analysis of the data from all clinical trials shows that only three of 84 anthracycline-naive patients developed heart failure during Herceptin therapy; these were elderly patients with pre-existing heart disease and all improved with standard therapy for heart failure.[56] Improvement in cardiac dysfunction with standard therapy has been observed in the majority of patients whether or not Herceptin was withdrawn. Importantly, the incidence of symptomatic cardiac dysfunction was only 1% when Herceptin was administered in combination with paclitaxel.[28,55]

Discussion

The limitations of cytotoxic chemotherapy, particularly in relation to continued disease control, toxicity, and the failure of manipulating dose and schedule and of novel cytotoxic combinations to improve survival have provided the impetus to develop a more rational, targeted approach to treating breast cancer. Targeting the HER2 oncogene is one of the first of these targeted approaches to reach the clinic for the treatment of advanced breast cancer. Herceptin, both alone and in combination with chemotherapy and when used as first-, second- or third-line therapy, has confirmed clinical benefit and a favorable toxicity profile in patients with $HER2^+$ MBC.[24,25,27–30] These benefits were obtained when Herceptin was administered until disease progression.

The use of chemotherapy until disease progression has been examined,[2] but has not entered standard practice, primarily due to the acute and chronic toxicity of conventional anticancer drugs and their impact on patient QoL. Features of Herceptin including its safety profile, positive impact on QoL and antitumor effects mean that different considerations apply. The importance of the duration of Herceptin therapy is demonstrated by preclinical studies revealing that withdrawal of Herceptin treatment is accompanied by tumor regrowth.[50] These data support the use of a Herceptin dose regimen that produces continuous therapeutic serum levels of the drug (4 mg/kg i.v. initial dose followed by 2 mg/kg i.v. weekly) until disease progression, as used in most reported clinical trials.

These trials have consistently demonstrated that Herceptin produces clinical benefits including increased survival duration and maintained or improved QoL, while being generally well tolerated. The approved indications (first-line therapy in combination with paclitaxel and second/third-line monotherapy for $HER2^+$ patients with MBC) ensure that the potential risks of Herceptin therapy, specifically cardiac dysfunction, are minimized. This has ensured that the risk:benefit ratio of Herceptin therapy is good in women who have particularly aggressive MBC due to HER2 abnormalities, although some have argued that the cardiac

events associated with Herceptin should be given more importance.[57] Furthermore, the use of Herceptin until disease progression in MBC results in drug-related mortality rates at least as good and probably better than those associated with chemotherapy (Roche, data on file).[55]

While existing data provide clear support for the use of Herceptin until disease progression, treatment beyond progression could be beneficial. Tripathy *et al.* have presented data from a recent analysis of patients who continued to receive Herceptin after disease progression in the pivotal phase III trial.[58] A total of 93 of 235 patients initially treated with Herceptin plus chemotherapy received Herceptin either alone or in combination with chemotherapy at disease progression at the discretion of the investigator. The response rate among these patients was 11% and response duration was 6.7 months. Furthermore, no new side effects of Herceptin were observed with up to 12 months of therapy, indicating that long-term exposure is well tolerated. The rationale for this approach lies in preclinical data indicating that Herceptin is effective against tumor cells as long as it is present, whereas Herceptin withdrawal results in rapid tumor re-growth.[50] Furthermore, the synergistic and additive effects of combinations of Herceptin with different chemotherapeutic agents may be at least in part due to different interactions between the mechanisms of action of Herceptin and the combination agent.[49,50] Due to these interactions, substituting one chemotherapeutic agent with another or adding chemotherapy to Herceptin monotherapy at disease progression may produce greater clinical benefit than could be expected if Herceptin were withdrawn and replaced with chemotherapy. These strategies require further investigation and clinical confirmation. These aspects of Herceptin use could be addressed in a study in which upfront Herceptin plus chemotherapy is compared with Herceptin monotherapy, with the addition or substitution of chemotherapy at progression. Preliminary data show that this approach may have value and further studies are currently being designed.[59]

Conclusions

Most available clinical data on Herceptin have been obtained using a regimen including a 4 mg/kg initial i.v. dose followed by 2 mg/kg i.v. weekly administered until disease progression. The clinical benefits of this regimen include a improvement in survival duration of up to 45% when Herceptin was administered in combination with chemotherapy as first-line therapy for $HER2^+$ MBC. Furthermore, the regimen was generally well tolerated and has a positive effect on QoL. The rationale for the use of this Herceptin regimen is based on both preclinical observations and the concept that continuous targeting of cells with a specific abnormality (HER2 amplification/overexpression) will produce continuous tumor growth suppression. Based on both preclinical and clinical data, there is a rationale to support investigation of continuing Herceptin beyond disease progression in the hope of obtaining further clinical benefits and providing the best opportunity for improved survival. This strategy will be investigated in new clinical trials.

References

1. Harris H, Morrow M, Norton L. Malignant tumors of the breast. In: DeVita Jr, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*, 5th edn. Philadelphia, PA: Lippincott-Raven 1997: 1557–616.
2. Buzdar AU, Michaud B, Hortobagyi GN. What is the optimal duration of chemotherapy in advanced breast cancer? In: *Abstr 10th Int Congr on Anti-Cancer Treatment* 2000: 45–7.
3. Coates A, Stat VGM, Bishop JF, *et al*. Improving the quality of life during chemotherapy for advanced breast cancer. *N Engl J Med* 1987; **317**: 1490–5.
4. Gregory RK, Powles TJ, Chang JC, Ashley S. A randomised trial of six versus twelve courses of chemotherapy in metastatic carcinoma of the breast. *Eur J Cancer* 1997; **33**: 2194–7.
5. Harris AL, Cantwell BMJ, Carmichael J, *et al*. Comparison of short-term and continuous chemotherapy (mitoxantrone) for advanced breast cancer. *Lancet* 1990; **335**: 186–90.
6. Muss HB, Case LD, Richards F, *et al*. Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. *N Engl J Med* 1991; **325**: 1342–8.
7. Norton L. Kinetic concepts in the systemic drug therapy of breast cancer. *Semin Oncol* 1999; **26**(suppl 2): 11–20.
8. Stockler M, Wilcken NRC, Ghersi D, Simes RJ. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev* 2000; **26**: 151–68.
9. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: overview of the randomised trials. *Lancet* 1998; **351**: 1451–67.
10. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: overview of the randomised trials. *Lancet* 1998; **352**: 930–42.
11. Akiyama T, Sudo C, Ogawara H, *et al*. The product of the human c-erbB-2 gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. *Science* 1986; **232**: 1644–6.
12. Ross JS, Fletcher JA. The HER-2/*neu* oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. *Stem Cells* 1998; **16**: 413–28.
13. Slamon DJ, Clark GM, Wong SG, *et al*. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science* 1987; **235**: 177–82.

14. Slamon DJ, Godolphin W, Jones LA, *et al*. Studies of the HER2/*neu* proto-oncogene in human breast and ovarian cancer. *Science* 1989; **244**: 707–12.
15. Hudziak RM, Schlessinger J, Ullrich A. Increased expression of the putative growth factor receptor p185^{HER2} causes transformation and tumorigenesis of NIH 3T3 cells. *Proc Natl Acad Sci USA* 1987; **85**: 7159–63.
16. Amici A, Venanzi FM, Concetti A. Genetic immunization against neu/erbB2 transgenic breast cancer. *Cancer Immunol Immunother* 1998; **47**: 183–90.
17. Brugger W, Brossart P, Scheding S, *et al*. Approaches to dendritic cell-based immunotherapy after peripheral blood stem cell transplantation. *Ann NY Acad Sci* 1999; **872**: 363–71.
18. Carter P, Presta L, Gorman CM, *et al*. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci USA* 1992; **89**: 4285–9.
19. Disis ML, Cheever MA. HER-2/*neu* oncogenic protein: issues in vaccine development. *Crit Rev Immunol* 1998; **18**: 37–45.
20. Jinno H, Ueda M, Enomoto K, *et al*. Effectiveness of adriamycin immunoconjugate that recognizes the c-erbB-2 product on breast cancer cell lines. *Surg Today* 1996; **26**: 501–7.
21. Park JW, Hong K, Carter P, *et al*. Development of anti-p185HER2 immunoliposomes for cancer therapy. *Proc Natl Acad Sci USA* 1995; **92**: 1327–31.
22. Rosenblum MG, Shawver LK, Marks JW, *et al*. Recombinant immunotoxins directed against the *c-erb-2/HER2/neu* oncogene product: *in vitro* cytotoxicity, pharmacokinetics, and *in vivo* efficacy studies in xenograft models. *Clin Cancer Res* 1999; **5**: 865–74.
23. Baselga J, Tripathy D, Mendelsohn J, *et al*. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *J Clin Oncol* 1996; **14**: 737–44.
24. Burstein HJ, Kuter I, Richardson PG, *et al*. Herceptin and navelbine for HER2-positive metastatic breast cancer: a phase II study. *Proc Am Soc Clin Oncol* 2000; **19**: 102a (abstr 392).
25. Cobleigh MA, Vogel CL, Tripathy D, *et al*. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999; **17**: 2639–48.
26. Pegram MD, Lipton A, Hayes DF, *et al*. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-over-expressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol* 1998; **16**: 2659–71.
27. Seidman A, Fornier M, Esteva FJ, *et al*. Final report: weekly Herceptin and Taxol for metastatic breast cancer: analysis of efficacy by HER2 immunophenotype (IHC) and gene amplification (FISH). *Proc Am Soc Clin Oncol* 2000; **19**: 83a (abstr 319).
28. Slamon D, 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**: 783–92.
29. Vogel C, Cobleigh M, Tripathy D, *et al*. First-line, non-hormonal, treatment of women with HER2 overexpressing metastatic breast cancer with Herceptin (trastuzumab, humanized anti-HER2 antibody). *Proc Am Soc Clin Oncol* 2000; **19**: 71a (abstr 275).
30. Vogel C, Cobleigh M, Tripathy D, *et al*. First-line single-agent Herceptin (H) therapy for women with HER2-overexpressing metastatic breast cancer (MBC). *Eur J Cancer* 2000; **36**(suppl 5): S53 (abstr 40).
31. Kuzur ME, Albain KS, Huntington MO, *et al*. A phase II trial of docetaxel and Herceptin in metastatic breast cancer patients overexpressing HER-2. *Proc Am Soc Clin Oncol* 2000; **19**: 131a (abstr 512).
32. Gilewski T, Norton L. Cytokinetics of neoplasia. In: Meldelsohn J, Howley P, Israel MA, *et al*., eds. *The molecular basis of cancer*. Philadelphia, PA: Saunders 1995: 143–59.
33. Wilcox WS, Schabel Jr FM, Skipper HE. Experimental evaluation of potential anticancer agents XV. On the relative rates of growth and host kill of 'single' leukemia cells that survive *in vivo* cytoxan therapy. *Cancer Res* 1966; **26**: 1009–14.
34. Hryniuk WM. Average relative dose intensity and the impact on design of clinical trials. *Semin Oncol* 1987; **14**: 65–74.
35. Peters WP, Jones RB, Vredenberg J, *et al*. A large, prospective, randomized trial of high-dose combination alkylating agents with autologous bone marrow support as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin-based induction therapy. *Proc Am Soc Clin Oncol* 1996; **15**: 121 (abstr 149).
36. Wood WC, Budman DR, Korzun AH, *et al*. Dose and dose intensity trial of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 1994; **330**: 1253–9.
37. Bonadonna G, Zambetti M, Valagussa P. Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. *J Am Med Ass* 1995; **273**: 542–7.
38. Henderson IC, Berry D, Demetri G, *et al*. Improved disease-free and overall survival from the addition of sequential paclitaxel but not from the escalation of doxorubicin dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 101a (abstr 390a).
39. Hudis C, Seidman A, Raptis G, *et al*. Sequential adjuvant therapy: the Memorial Sloan-Kettering Cancer Center experience. *Semin Oncol* 1996; **23**: 58–64.
40. Perloff M, Norton L, Koruzun AH, *et al*. Postsurgical adjuvant chemotherapy of stage II breast carcinoma with or without crossover to a non-cross-resistant regimen: A Cancer and Leukemia Group B study. *J Clin Oncol* 1996; **14**: 1589–98.
41. Ackland SP, Gebski V, Wilson A, *et al*. High dose epirubicin cyclophosphamide (HDEC) with filgrastim versus standard dose (SDEC) in advanced breast cancer—a quality of life study by the ANZ Breast Cancer Trials Group. *Proc Am Soc Clin Oncol* 2000; **19**: 75a (abstr 288).

42. Muss HB, Thor AD, Berry DA, *et al*. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. *N Engl J Med* 1994; **330**: 1260–6.
43. Seidman AD, Baselga J, Yao TJ, *et al*. HER-2/*neu* overexpression and clinical taxane sensitivity: a multivariate analysis in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol* 1996; **15**: 104 (abstr 80).
44. Lonning PE. Is there a growing role for endocrine therapy in the treatment of breast cancer? *Drugs* 2000; **60**: 11–21.
45. Ejlertsen B, Pfeiffer P, Pederson D, *et al*. Decreased efficacy of cyclophosphamide, epirubicin, and 5-fluorouracil in metastatic breast cancer when reducing treatment duration from 18 to 6 months. *Eur J Cancer* 1993; **29A**: 527–31.
46. Pegram MD, Baly D, Wirth C, *et al*. Antibody dependent cell-mediated cytotoxicity in breast cancer patients in phase III clinical trials of a humanized anti-HER2 antibody. *Proc Am Ass Cancer Res* 1997; **38**: 602.
47. Sliwkowski MX, Lofgren JA, Lewis GD, *et al*. Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin). *Semin Oncol* 1999; **26**(suppl 12): 60–70.
48. Baselga J, Norton L, Albanell J, *et al*. Recombinant humanized anti-HER2 antibody (Herceptin®) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/*neu* overexpressing human breast cancer xenografts. *Cancer Res* 1998; **58**: 2825–31.
49. Pegram M, Hsu S, Lewis G, *et al*. Inhibitory effects of combinations of HER-2/*neu* antibody and chemotherapeutic agents used for treatment of human breast cancers. *Oncogene* 1999; **18**: 2241–51.
50. Pietras RJ, Pegram MD, Finn RS, *et al*. Remission of human breast cancer xenografts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs. *Oncogene* 1998; **17**: 2235–49.
51. Lieberman G, Burchmore MJ, Ferhenbacher L, Cobleigh M. Health related quality of life of patients with HER-2 overexpressing metastatic breast cancer treated with Herceptin® (trastuzumab) as a single agent. *Proc Am Soc Clin Oncol* 1999; **18**: 417a (abstr 1613).
52. Osoba D, Burchmore M, Ash M, *et al*. Health related quality of life (HRQL) of patients with first-line, single agent, trastuzumab (Herceptin) for metastatic HER-2 overexpressing breast cancer. *Proc Am Soc Clin Oncol* 2000; **19**: 436a (abstr 1710).
53. Mass RD, Sanders C, Kasian C, *et al*. The concordance between the clinical trials assay (CTA) and fluorescence in situ hybridization (FISH) in the Herceptin pivotal trials. *Eur J Cancer* 2000; **36**(suppl 5): S52 (abstr 38).
54. Baselga J, Kerrigan M, Burchmore M, Ash M. Health-related quality of life (HRQL) in women with HER2-overexpressing metastatic breast cancer (MBC) in a phase III study of Herceptin (R) plus chemotherapy versus chemotherapy alone. *Eur J Cancer* 1999; **35**(suppl 4): S318 (abstr 1276).
55. Baselga J. Safety profile of Herceptin (H) as a single agent and in combination with chemotherapy. *Eur J Cancer* 1999; **35**(suppl 4): S324 (abstr 1299).
56. Cook-Bruns N. Retrospective analysis of the safety of Herceptin® immunotherapy in metastatic breast cancer. *Oncology* 2001; in press.
57. Feldman AM, Lorell BH, Reis SE. Trastuzumab in the treatment of metastatic breast cancer: anticancer therapy versus cardiotoxicity. *Circulation* 2000; **102**: 272–4.
58. Tripathy D, Slamon D, Leyland-Jones B, *et al*. Treatment beyond progression in the Herceptin pivotal combination chemotherapy trial. *Breast Cancer Res Treat* 2000; **64**: 32 (abstr 25).
59. Burris III HA, Hainsworth JD, Miranda FT, *et al*. Phase II trial of Herceptin induction followed by combination therapy with paclitaxel and carboplatin: a Minnie Pearly Research Network Trial. *Breast Cancer Res Treat* 2000; **64**: 31 (abstr 24).

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